Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende andexanet alfa til behandling af patienter, som modtager direkte faktor Xa-hæmmer og har livstruende eller ukontrolleret blødning

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. andexanet alfa, version 1.0
2. Forhandlingsnotat fra Amgros vedr. andexanet alfa
3. Høringssvar fra ansøger, inkl. eventuel efterfølgende dialog vedr. lægemidlets værdi og den sundhedsøkonomiske afrapportering
4. Medicinrådets vurdering vedr. andexanet alfa til behandling af behandling af patienter, som modtager direkte faktor Xa-hæmmer og har livstruende eller ukontrolleret blødning, version 1.0
5. Ansøgers endelige ansøgning
6. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
7. Medicinrådets protokol for vurdering vedr. andexanet alfa til behandling af behandling af patienter, som modtager direkte faktor Xa-hæmmer og har livstruende eller ukontrolleret blødning, version 1.0

Medicinrådet

Medicinrådets sundhedsøkonomiske afrapportering

Andexanet alfa

Revertering af antikoagulation på grund af livstruende eller ukontrolleret blødning

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner. Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling og udarbejder fælles regionale behandlingsvejledninger. Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

Dokumentets formål

Den sundhedsøkonomiske analyse indeholder Medicinrådets vurdering af de inkrementelle omkostninger pr. patient og budgetkonsekvenserne ved anbefaling. Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Den sundhedsøkonomiske analyse er udarbejdet efter Metodevejledning for omkostningsanalyse af nye lægemidler og indikationsudvidelser i hospitalssektoren.

Dokumentoplysninger	
Godkendelsesdato	23. juni 2021
Dokumentnummer	117299
Versionsnummer	1.0

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 23. juni 2021

Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DOAK	Direkte orale antikoagulantia
DRG	Diagnose Relaterede Grupper
FXa-hæmmer	Direkte faktor Xa-hæmmere
ISTH	*International Society on Thrombosis and Haemostasis*
PKK	Protrombinkomplexkoncentrat
SAIP	Sygehusapotekernes indkøbspriser

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for andexanet alfa ca. [redacted] DKK pr. patient sammenlignet med PKK. Når analysen er udført med apotekets indkøbspriser (AIP), er de inkrementelle omkostninger til sammenligning ca. 152.000 DKK pr. patient.

Lægemiddeldosis for både andexanet alfa og PKK kan variere for patienterne, og derfor er der usikkerhed forbundet med den anvendte dosis i hovedanalysen. I en følsomhedsanalyse undersøges omkostningerne ved at øge dosis for andexanet alfa til det maksimale og ved at sænke dem til det mindst mulige. Her bliver de inkrementelle omkostninger hhv. [redacted] DKK og [redacted] DKK.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af andexanet alfa som mulig standardbehandling vil være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 33,4 mio. DKK i år 5.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af andexanet alfa som mulig standardbehandling på danske hospitaler til patienter, som modtager direkte faktor Xa-hæmmer og har livstruende eller ukontrolleret blødning.

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Alexion. Vi modtog ansøgningen den 11. december 2021.

3.1 Patientpopulation

Andexanet alfa er rettet mod revertering af en undergruppe af direkte orale antikoagulantia (DOAK), kaldet direkte faktor Xa-hæmmere (FXa-hæmmer), herunder specifikt de to mest anvendte DOAKs i Danmark, rivaroxaban og apixaban. Fagudvalget anslår, at ca. 80.000 patienter er i behandling med rivaroxaban og apixaban. Under antagelse af en hændelsesrate for alvorlige blødninger på 2-3,5 % vil 1.600-2.800 patienter årligt få alvorlig direkte FXahæmmerassocieret blødning. Heraf vil kun en lille andel have livstruende eller ukontrollerede blødninger og dermed være kandidater til akut reverteringsbehandling.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af andexanet alfa på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvad er værdien af andexanet alfa sammenlignet med protrombinkomplexkoncentrat til patienter, som modtager direkte faktor Xa-hæmmer og har livstruende eller ukontrolleret blødning?

4. Vurdering af den sundhedsøkonomiske analyse

I sin ansøgning har ansøger indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for andexanet alfa sammenlignet med protrombinkomplexkoncentrat (PKK). Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for model

Ansøger har sammenlignet med PKK på baggrund af data fra ANNEXA-4 studiet [1]. Det er et single-arm fase III-studie fra 2019, hvor patienter har modtaget behandling med andexanet alfa. ANNEXA-4 studiet er ved *propensity score matching* analyse sammenlignet med de to studier ORANGE [2] og RETRACE II [3,4], hvor patienterne i begge studier modtog behandling med PKK. Derudover anvender ansøger flere andre studier til at estimere effekten af behandling med PKK [5,6].

4.1.1 Modelbeskrivelse

Ansøger har indsendt et beslutningstræ og en Markov model til at estimere omkostningerne forbundet med behandlingen med andexanet alfa. Patienterne i behandling med enten andexanet alfa eller PKK begynder i beslutningstræet, der har til formål at estimere omkostningerne ved de første 30 dages behandling, hvor sygdommen er meget akut.

Beslutningstræet

Alle patienter, der træder ind i modellen, vil opleve en større akut blødning, hvor de relaterede omkostninger til blødningseventet og behandlingen vil blive opfanget. Det antages ikke, at andexanet alfa vil påvirke frekvensen af blødninger, men udelukkende i form af tid til hæmostase. Derfor antages det i modellen at patienter kun oplever én blødning. Patienter, der overlever blødningen, vil fortsætte til Markov modellen, som har til formål at opfange langtidsomkostningerne til senfølger efter de akutte blødninger.

Patienter, der oplever en akut blødning, bliver enten behandlet med andexanet alfa eller PKK. Sandsynligheden for at overleve afhænger i modellen af hvilken behandling patienten modtager. Mortalitetsraterne for at overleve en blødning er for enkelte blødningstyper baseret på data fra ANNEXA-4 studiet, mens størstedelen af mortalitetsraterne for overlevelse efter en blødning er estimeret af en dansk klinisk ekspert.

Markov modellen

De patienter der overlever efter 30 dage i beslutningstræet, vil fortsætte ind i Markov modellen, som skal estimere forskellen i omkostninger til senfølger efter en større blødning.

Ansøger argumenterer, på baggrund af en udtalelse fra en dansk klinisk ekspert, at graden af senfølger efter en blødning, påvirkes af alvorligheden og længden af blødningen. Der argumenteres for at omkostninger til senfølger af denne grund vil være forskellige mellem andexanet alfa og PKK, da der er en forventning om at andexanet alfa stopper blødninger mere effektivt. Ansøger redegør for, at det er svært at finde direkte sammenlignelige studier til at sammenligne andexanet alfa og PKK-behandling, da effektiv hæmostase bør måles i overensstemmelse med *International Society on Thrombosis and Haemostasis (ISTH)* nye standard kriterie og dette er ikke tilfældet for de fleste studier omhandlende behandling med PKK. I de studier ansøger mener er mest sammenlignelig med ANNEXA-4 studiet, er klinisk hæmostase beskrevet som værende fremragende eller god ved 68 % og 72 % af patienterne behandlet med PKK [5,6]. I ANNEX-4 studiet var det til sammenligning tilfældet ved 82 % af patienterne.

Baseret på en forventning om at andexanet alfa vil være mere effektivt end PKK-behandling til at stoppe blødninger, estimerer en klinisk ekspert fra Storbritannien, at behandlingen med andexanet alfa vil være 25% mere effektiv til at hindre senfølge i forbindelse med større blødninger. Ansøger har ikke kunne få et tilsvarende estimat fra en dansk klinisk ekspert og vælger derfor et mere konservativt estimat i deres analyse, hvor de estimerer at andexanet alfa vil medføre en 20% reduktion i senfølger sammenlignet med PKK.

Medicinrådets vurdering af ansøgers modelantagelser

Ansøger har indsendt en analyse der er baseret på meget usikre data. Dele af analysen baserer sig alene på en enkelt klinikers forventning til effekten af andexanet alfa, dette til trods for, at de har udført en *popensity score matching* analyse. Den 20 % reduktion i senfølger som ansøger har estimeret på baggrund af en enkelt klinikers forventning til andexanet alfa, anvendes flere steder i analysen. Estimatet benyttes også til at beregnes den gennemsnitlige indlæggelsestid for patienterne, hvor det antages at indlæggelsestiden reduceret med 20 % for andexanet alfa.

Ansøgers sammenligning af andexanet alfa og PKK lavet i form af *propensity score matching* er i vurderingsrapporten fundet meget usikker og bør ikke drive den sundhedsøkonomiske analyse. Årsagen hertil er bl.a. at patienterne med dårligst prognose ikke er inkluderet i ANNEXA-4 studiet. En uddybende beskrivelse af usikkerhederne ved den udførte *propensity score matching* kan ses i vurderingsrapporten.

Fagudvalget vurderer, at det ud fra det foreliggende datagrundlag ikke er muligt at vurdere, om andexanet alfa sammenlignet med komparatoren PKK er et bedre, dårligere eller ligeværdigt behandlingsalternativ. Grundet mange meget usikre estimater i ansøgers analyse vil analysen ikke blive præsenteret yderligere. I stedet for udfører Medicinrådet egen hovedanalyse, hvor kun omkostninger til lægemidler vil blive inkluderet.

Medicinrådet accepterer ikke ansøgers tilgang vedr. modelantagelser. Medicinrådet udfører en simpel omkostningsanalyse, hvor kun omkostninger til lægemidler vil være inkluderet.

4.2 Omkostninger

Som det er nævnt tidligere, vil ansøgers analyse ikke blive præsenteret, da denne bygger på meget usikkert datagrundlag, der kan medføre at resultatet af analysen ikke vil være retvisende. MR udfører i stedet en simpel analyse hvor lægemiddelomkostninger til behandlingen med andexanet alfa og PKK er estimeres.

Analysen er baseret lægemiddeldoser på Medicinrådets protokol. Se Tabel 1.

Medicinrådet har udskiftet AIP med sygehusapotekets indkøbspris (SAIP), se Tabel 1.

Tabel 1. Anvendte lægemiddelpriser, SAIP, (februar 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Betingede pris [DKK]	Kilde
Andexanet alfa	200 mg	4 stk.	[redacted]	[redacted]	Amgros
PKK	500 IE	1 stk.	[redacted]		Amgros
	1000 IE	1 stk.	[redacted]		Amgros

[redacted]

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen og de økonomiske konsekvenser af at justere de parametre, der er usikre.

Andexanet alfa kan gives ved høj og lav dosis. Ved anvendelse af høj dosis fordobles lægemiddelomkostningerne. I medicinrådets hovedanalyse antages 50 % af patienterne at modtage høj dosis og 50 % at modtage lav dosis.

I følsomhedsanalyser vil betydningen af dosis blive undersøgt. Her laves to scenarier; ét hvor alle patienter modtager højeste dosis af andexanet alfa og laveste dosis af PKK, og ét hvor alle patienter modtager laveste dosis af andexanet alfa og højeste dosis af PKK. De to scenarier udgør således den maksimale og minimale omkostning.

4.4 Opsummering af basisantagelser

I Tabel 2 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 2. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	21 år	Behandlingsforløb for én blødning
Diskonteringsrate	4 %	Ikke aktuel
Inkluderede omkostninger	Lægemiddelomkostninger Administrationsomkostninger Monitoreringsomkostninger Patientomkostninger	Lægemiddelomkostninger
Dosering:		
Andexanet alfa	16% høj dosis 84% lav dosis	50% høj dosis 50% lav dosis
PKK	25 IE/kg	50% høj dosis (50 IE/kg) 50% lav dosis (25 IE/kg)

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på lægemiddelomkostninger, og antagelserne i analysen fremgår af Tabel 2.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. [redacted] DKK i Medicinrådets hovedanalyse.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. 152.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 3.

Tabel 3. Resultatet af Medicinrådets hovedanalyse ved sammenligning med PKK, DKK

	Andexanet alfa	PKK	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 4.

Tabel 4. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
Maksimal omkostning ved andexanet alfa	[redacted]
Minimal omkostning ved andexanet alfa	[redacted]

6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at andexanet alfa vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier:

- Andexanet alfa bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Andexanet alfa bliver ikke anbefalet som mulig standardbehandling.

Budgetkonsekvenserne udgør forskellen mellem de samlede omkostninger i de to scenarier.

6.1 Medicinrådets estimat af patientantal

Fagudvalget er blevet konsulteret i forhold til patientantal, hvis andexanet alfa anbefales som mulig standardbehandling, og hvis ikke andexanet alfa anbefales. Fagudvalget estimerer, at 160 – 280 patienter pr. år forventes at være kandidater til behandling med andexanet alfa til den pågældende indikation. Fagudvalget fremhæver dog, at dette estimat er forbundet med nogen usikkerhed, særligt da estimatet forudsætter, at anvendelsen af andexanet alfa udelukkende forbeholdes den godkendte indikation. På baggrund af det estimerede patientantal bliver Medicinrådets budgetkonsekvensanalyse baseret på et årligt antal patienter på 220 og et markedsoptag på 100%.

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet estimerer, at anvendelse af andexanet alfa vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 5.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 33,4 mio. DKK i det femte år efter en anbefaling.

Tabel 5. Medicinrådets analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7. Diskussion

Behandling med andexanet alfa er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med behandling med PKK.

Lægemiddeldosis for både andexanet alfa og PKK kan variere for patienterne, og derfor er der usikkerhed forbundet med den anvendte dosis i hovedanalysen. I en følsomhedsanalyse undersøges omkostningerne ved at øge dosis for andexanet alfa til det maksimale og ved at sænke dem til det mindst mulige. Her bliver de inkrementelle omkostninger hhv. [redacted] DKK og [redacted] DKK.

Fagudvalget vurderer, at der er risiko for indikationsskred ved behandling med andexanet alfa, da det akutte setting ofte ikke tillader en vurdering af, om en given patient er omfattet af indikationen, og hvilket doseringsprogram der bør følges. Det vil derfor ofte i praksis blive anvendt i den høje dosis og til flere patienter, end de der er behandlet med rivaroxaban og apixaban.

Da analysen begrænser sig til kun at indeholde omkostninger til lægemidlerne, vil der være usikkerheder forbundet med den samlede behandlingsomkostning. Hvis andexanet alfa reducerer indlæggelsestiden på hospitalet og omfang af senfølger efter en større blødning, så vil dette reducere den inkrementelle omkostning, men da der ikke er indsendt evidens for dette, er der ikke taget højde for en eventuel effektforskel i analysen. De inkrementelle omkostninger kan derfor være overestimerede.

8. Referencer

1. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med [internet]. 2019 [citeret 17. marts 2021];380(14):1326–35. Tilgængelig fra: http://www.nejm.org/doi/10.1056/NEJMoa1814051

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Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

Forhandlingsnotat

Dato for behandling i Medicinrådet	23.06.2021
Leverandør	Alexion
Lægemiddel	Andexanet alfa (Ondexxya)
Ansøgt indikation	Revertering af antikoagulation på grund af livstruende eller ukontrolleret blødning.

Forhandlingsresultat

Amgros har opnået følgende **betingede pris** på andexanet alfa:

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Andexanet alfa	200 mg	4 stk.	95.000	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

Vurdering af forhandlingsresultatet

Det er Amgros' vurdering, at vi på nuværende tidspunkt har opnået den bedst mulige pris på andexanet alfa.

Konklusion

Det er Amgros vurdering at vi har opnået den bedst mulige pris på andexanet alfa.

[redacted]

Relation til markedet

Der er på nuværende tidspunkt ingen konkurrence på området.

Status fra andre lande

Norge: Under behandling, afventer indsendelse af dokumentation fra producent[1].

Sverige: NT-rådet valgte i oktober 2020 ikke at anbefale andexanet alfa til reversering af antikoagulation på grund af livstruende eller ukontrolleret blødning[2].

UK: NICE valgte i maj 2021 at anbefale andexanet alfa som mulig standardbehandling til patienter med gastrointestinale blødninger[3].

[1] Andexanet alfa (Ondexxya) (nyemetoder.no)
[2] https://janusinfo.se/download/18.7780a96c175025c97dbdaeb8/1603108441830/Ondexxya 2020-10-16.pdf
[3] Andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban (nice.org.uk)

Attention:
Medicines Council
Dampfærgevej 27-29, 3.th
2100 København Ø

29/04/2021

Consultancy Response

50/50 dosing not supported by clinical evidence

Medicinrådet assumed that approximately 50% of patients will receive low dose andexanet and 50% of patients will receive high dose andexanet**.** This is not supported by clinical evidence. Based on the included publications in the assessment report, low dose scheme varies between 73% and 89% of the patient populations. From the ANNEXA-4 final report, dosing schemes can be identified in figure 2 (84% received low dose).

When diverging from the dosing scheme used in the study it is important to stress that this also undermines the use of the results from the study as the efficacy results from the study is directly linked to the dosage received. There is no evidence available for the 50/50 dosing split used in the base case of Medicinrådet, hence this approach introduces further uncertainty in the assessment of the clinical efficacy while adding additional costs to Andexanet.

Dosing schemes of andexanet were also investigated thoroughly in the US chart audit. This data assessment was part of a follow-up and not included the Coleman publication which we submitted to Medicinrådet. 71% of the 1618 andexanet patients received low dose in this follow-up analysis. There were slight differences for the various bleed types; GI 73%, ICH 71%, critical compartment 64% and other bleeds 92%. This can be further confirmed by the European countries where Ondexxya has been implemented in clinical practice.

All patients treated with apixaban for atrial fibrillation should be eligible for low dose andexanet since no patient is treated with more than 5 mg of apixaban according to Danish guidelines and confirmed by a Danish cardiologist. The same is true for apixaban as VTE-prophylaxis, except for the first 10 days of treatment. It's also worth noting that in recent years there has been an increasing use of long-term low dose apixaban and rivaroxaban for prevention of PE/VTE according to new European guidelines. For the time being, apixaban and rivaroxaban are almost equally prescribed to Danish patients.

If patients had their last FXa-inhibitor equally or more than 8 hours ago, they would automatically fall into the low dose andexanet category. It is very unlikely that high dose andexanet must be used because the treating physician is not able to identify at least one parameter - apixaban/rivaroxaban dose or time since last dose.

Lack of evidence for PCC as an off-label treatment

4F-PCC is licensed for urgent reversal of VKAs in adults with acute major bleeding and works well in that setting. There is no mechanistic rationale that PCCs would work for the reversal of Factor Xa-inhibitors. The presumed theory is that by adding FII and FX some of the Factor Xa-inhibition can be overruled. PCCs have not demonstrated effect on anti FXa activity and shows a delayed effect on thrombin generation in healthy volunteers treated with FXa-inhibitors[1]. In-vitro assays demonstrate that PCCs can only generate thrombin at subtherapeutic levels of rivaroxaban and apixaban and that

the 4F-PCC dose required to overcome therapeutic levels of FXa inhibitor via this mechanism would be 20×higher than the highest approved dose[2].

PCCs were originally designed to replete Factor IX deficiency in Hemophilia B patients which explains the standardization of Factor IX in these concentrates. Concentrations of Factor II, VII and X and other additives may vary. PCC dose which is efficacious and safe for the reversal of FXa-inhibitors is not established. Dose varied greatly in the three publications included in the assessment report.

Although many case series describing the use of PCCs for managing DOAC-related bleeds have been published, the presence of common methodological flaws in both objective assessments of outcome and series analyses necessitates caution in their interpretation. For example, only a small proportion of PCC trials identified in the Danish assessment report used ISTH criteria to assess hemostatic efficacy. For that reason, the results must be interpreted with great uncertainty as noted also by the Danish expert committee. An additional aspect is that PCC more seldom is administered as a single agent but rather part of an optimized standard of care. This can include for example blood products, fluid substitution, plasma expanders or prothrombin concentrates. Standard of care may differ depending on application and bleed type. I the US real world chart audit andexanet alfa was used as a single agent in 83% of patient cases in comparison to 72% of patients in 4F-PCC cohort. For this reason, it's even more complicated to assess safety and efficacy of PCC alone.

The preference towards a specific reversal agent is reflected across many international guidelines, from different medical specialties. PCCs would only be the treatment of choice if a specific reversal agent is not available. A recent example is the EHRA guideline update from April 2021:

Life threatening- or bleeding in to critical site
For Factor Xa-inhibitor treated patients: Andexanet alfa (dosing see fig.X)
Otherwise consider PCC 50 U/kg +25U/kg if indicated or aPCC 50 U/kg + max 200 U/kg/day

1. Song et al. J Thromb Haemost 2017;15:2125-2137
2. Lu et al. *Res Pract Thromb Haemost* 2020;00:1–13

Even though it is stated in the assessment report that a formal categorization of the clinical value of andexanet alfa compared to current clinical practice (PCC) according to Medicinrådets methods could not be carried out, the expert committee (fagudvalget) and the secretariat has chosen to base their calculations on an instant 100% market uptake. This sends a clear signal that there is an unmet need for specific reversal agents and that Andexanet alfa will be the preferred option.

Mortality benefit with andexanet

Medicinrådet concluded that mortality is a critical measure. Given the difficulties of objective hemostatic efficacy assessment in the PCC observational trials, the mortality measure may play an even more important role. However, it is critical to understand the clinical factors that increased mortality observation across baseline bleeding subtypes and comorbidities as this may account for important differences in observation. 30-day mortality varied between 14% and 24% in the included andexanet publications of the assessment report. For PCC it varied between 23,1% and 33%.

It was noted in the assessment report that andexanet seems to have a good effect on the critical measure mortality in a selected patient population with already good prognosis.

Alexion included a real-world study published by Coleman et al. in the revised dossier. The study did not exclude patients with an expected survival of less than 1 month, like ANNEXA-4. It can be noted that in-hospital mortality in the real-world study was lower than in ANNEXA-4, even though an exclusion criterion based on expected survival was not applied. If ANNEXA-4 only included only patients with a good prognosis one would expect a worse outcome in the RWE material which clearly wasn't the case. This could potentially support the generalizability of the trial outcomes to a broader population as noted also by the Ondexxya UK NICE appraisal.

Mortality benefit : subgroups

ANNEXA-4 clearly demonstrates that haemostatic efficacy for an ICH is a relevant clinical outcome associated with mortality improvement:

In an i**ntracranial haemorrhage** sub-analysis, haemostatic efficacy was assessed through minimisation of haematoma expansion between baseline and 12 hours. Andexanet alfa resulted in effective haemostasis in 79% (95% CI, 69.1-86.2) of patients with spontaneous ICH and in 83% (95% CI, 72%-91%) of patients with traumatic ICH[1,2].

Further minimisation of haematoma expansion was observed in a proportion of patients with intracerebral haemorrhage who were at high risk of haematoma expansion, given their short median time from symptom to baseline scan of 3.1 hours (1.3-6.2 IQR) and initial baseline haematoma volumes[3].

The mortality benefit for andexanet alfa can be seen with increasing baseline intracerebral haemorrhage volumes in patients with spontaneous intracerebral bleeding, the mortality rate in patients at the highest quartile of hematoma volumes (5 of 24; 20.8%) was not dissimilar to the overall mortality rate (16 of 99; 16.2%) (Appendix A) indicating that andexanet alfa improves mortality outcomes in patients with the most severe bleeding.

In contrast PCCs have not shown to be effective in minimising haematoma expansion nor have any mortality benefit[4].

Furthermore, ANNEXA-4 demonstrates that haemostatic efficacy for a **GI bleed** is a relevant clinical outcome which is associated with mortality improvement:

Patients with upper GI bleeding in ANNEXA-4 had a mean Glasgow Blatchford score of 13, suggesting that they were at high risk (95%) of requiring intervention or death. For upper GI bleeding mortality prognostic scores, the clinical pre-endoscopic Rockall score predicted a 39.6% mortality rate (Appendix B).

The 30-day mortality rate of 13% observed in ANNEXA-4 for upper GI patients suggests a magnitude of benefit of 68% which is consistent (if not slightly higher) than that predicted in the propensity score matching analysis (~50%).

Given the haemostatic results observed for andexanet alfa in ANNEXA-4, a mortality and morbidity benefit is to be expected, and was indeed observed.

To explore the implications of the ANNEXA-4 results, evidence from the US real-world analysis of patients receiving andexanet alfa within its licensed indication were assessed.

As shown in Appendix C, the baseline characteristics of the populations were similar between the ANNEXA-4 study and the real-world analysis, which supports that the eligibility criteria in the ANNEXA-4 study did not enrol an inherently different population to that which would be expected in clinical practice.

Furthermore, in-hospital mortality outcomes from the real-world analysis are consistent with those observed in the ANNEXA-4 study:

- **ICH mortality was 11.9% in the real-world analysis versus 11.0% in ANNEXA-4**
- **GI mortality was 3.1% in the real-world analysis versus 7.9% in ANNEXA-4**

Results from the real-world experience with andexanet alfa demonstrate that the mortality outcomes seen in the ANNEXA-4 study are reflective of what can be expected in clinical practice.

1 Goldstein J, Demchuk A, Zotova E, et al. Hemostatic Efficacy and Anti-fXa Reversal With Andexanet Alfa in Spontaneous Intracranial Hemorrhage. Poster Presented at NCS 2019; Vancouver, British Columbia; October 15-18, 2019.; 2019.

2 Milling T, Yue P, Zotova E, et al. Efficacy and Safety Outcomes in FXa-Associated Bleeding Following Trauma: An ANNEXA-4 Sub-study. Poster Presented at NCS 2019; Vancouver, British Columbia; October 15-18, 2019.; 2019.

3 Concha M, Yue P, Curnutte J, et al. Clinical Factors Associated With the Achievement of Hemostatic Efficacy in Patients With Intracranial Hemorrhage: An ANNEXA-4 Sub-study. Poster Presented at NCS 2019; Vancouver, British Columbia; October 15-18, 2019.; 2019.

4 Gerner ST, Kuramatsu JB, Sembill JA, et al. Association of prothrombin complex concentrate administration and hematoma enlargement in non-vitamin K antagonist oral anticoagulant-related intracerebral hemorrhage. *Annals of neurology.* 2018;83(1):186-196.

Medicinrådet

Medicinrådets vurdering af andexanet alfa til behandling af patienter, som modtager direkte faktor Xa-hæmmer og har livstruende eller ukontrolleret blødning

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om vurderingsrapporten

Vurderingsrapporten indeholder Medicinrådets vurdering af, hvilken værdi lægemidlet har for patienten i forhold til nuværende standardbehandling.

Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Lægemidlet er vurderet efter *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Dokumentoplysninger	
Godkendelsesdato	28. april 2021
Dokumentnummer	112850
Versionsnummer	1.0

Indholdsfortegnelse

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 28. april 2021

1. Medicinrådets konklusion

Medicinrådet finder, at den samlede værdi af andexanet alfa sammenlignet med nuværende standardbehandling i form af protrombinkomplekskoncentrat (PKK) ikke kan kategoriseres i henhold til Medicinrådets metode.

Ud fra det foreliggende datagrundlag er det ikke muligt at konkludere, om andexanet alfa er en lige så god og sikker behandling som komparatoren PKK.

Medicinrådet lægger vægt på bekymringen for forkert anvendelse på grund af praktiske udfordringer ved håndteringen, som i kombination med den forhøjede risiko for trombose udgør en risiko for patienterne i forhold til behandling med PKK.

MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

- **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.
- **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.
- **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.
- **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

I nogle situationer er det ikke muligt at kategorisere lægemidlets samlede værdi. De situationer opstår, når evidensgrundlaget for vurderingen er for usikkert til at kategorisere værdien jf. Medicinrådets metoder (f.eks. på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

MEDICINRÅDET VURDERER KVALITETEN AF DE DATA, DER LIGGER TIL GRUND FOR VURDERINGEN AF LÆGEMIDLET (EVIDENSENS KVALITET) I EN AF FØLGENDE GRADE-KATEGORIER:

- **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.
- **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.
- **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.
- **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.

2. Begreber og forkortelser

AK: Antikoagulation

CI: Konfidensinterval

DOAK: Direkte orale antikoagulantia

EMA: Det Europæiske Lægemiddelagentur *(European Medicines Agency)*

EPAR: *European Public Assessment Report*

GRADE: System til at vurdere evidens *(Grading of Recommendations, Assessment, Development and Evaluation*)

HR: *Hazard ratio*

ISTH: *International Society on Thrombosis and Haemostasis*

ITT: *Intention to treat*

OR: *Odds ratio*

PICO: Population, intervention, komparator og effektmål *(Population, Intervention, Comparator and Outcome)*

PKK: Protrombinkomplexkoncentrat

PP: *Per Protocol*

RCT: Randomiseret kontrolleret studie *(Randomised Controlled Trial)*

RR: Relativ risiko

SMD: *Standardized Mean Difference*

3. Introduktion

Formålet med Medicinrådets vurdering af andexanet alfa til patienter, som modtager direkte faktor Xa-hæmmer og har livstruende eller ukontrolleret blødning, er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Alexion Pharma. Medicinrådet modtog ansøgningen den 24. august 2020, som er blevet suppleret med data den 11. december 2020.

Det kliniske spørgsmål er:

Hvad er værdien af andexanet alfa sammenlignet med protrombinkomplexkoncentrat til patienter, som modtager direkte faktor Xa-hæmmer og har livstruende eller ukontrolleret blødning?

3.1 Livstruende og ukontrollerede blødninger

Blodets evne til at størkne, koagulationen, er en nøje reguleret proces, som aktiveres ved vævsskader. Blodkoagulationen er kompleks og består af en kaskade af reaktioner, der aktiveres for at stoppe blødninger. Koagulationssystemet består både af en cellulærkomponent (blodplader) og en proteinkomponent (koagulationsfaktorer). I tillæg til koagulationsfaktorerne er der ligeledes en række proteiner, der fungerer regulerende for koagulationen. Normalt er der en balance mellem disse processer, som forhindrer omfattende blødninger eller uønsket blodpropdannelse. Ved ubalance i systemet vil man enten få en blødningstendens, så man bløder lettere, og blødningerne standser ikke så hurtigt som normalt, eller man kan få en øget risiko for blodpropper.

Antikoagulationsbehandling (AK-behandling) gives til patienter med en øget risiko for at danne blodpropper, f.eks.: 1) ved forebyggelse af slagtilfælde hos patienter med atrieflimmer og/eller kunstige hjerteklapper; 2) ved behandling og sekundær forebyggelse af venøse blodpropper eller; 3) ved forebyggelse af venøse blodpropper hos patienter i øget risiko, f.eks. grundet operation [1]. De forskellige AK-behandlinger adskiller sig ved, hvor de indvirker på koagulationskaskaden for at modvirke, at patienten danner blodpropper. AK-behandling giver en øget blødningstendens, herunder en øget risiko for morbiditet og mortalitet som følge af alvorlige blødninger. Blødninger kan være alvorlige, hvis patienten mister meget blod, eller hvis blødningen opstår et kritisk sted, f.eks. i kraniet eller øjet.

Oral AK-behandling kan bestå af enten et direkte oralt antikoagulantium (DOAK) eller en vitamin K-antagonist (VKA-behandling). Risikoen for en alvorlig blødning varierer mellem forskellige AK-behandlinger. Generelt rapporterer studier lavere blødningsfrekvens, og særligt en reduktion i intrakranielle blødninger, ved DOAK-behandling end ved VKA-behandling [2]. På baggrund af at DOAK-behandling har vundet stort indpas [3], er DOAK-associerede blødninger dog en voksende problematik.

Randomiserede undersøgelser og observationelle studier har fundet, at alvorlige blødninger sker i 2-3,5 % af alle patienter pr. år behandlet med DOAK. Risikoen for intrakranielle blødninger anslås til ca. 0,3-0,5 % pr. patientår [4,5]. Gastrointestinale blødninger udgør op til 56 % af de alvorlige blødninger hos patienter i DOAK-behandling, hvorimod intrakranielle blødninger udgør en mindre andel, ca. 8-16 %[1].

Patienter med øget risiko for trombose, som er i AK-behandling og får en alvorlig blødning, har en stærkt øget dødelighed og risiko for trombose, når AK-behandlingen pauseres eller reverseres. Patienter med atrieflimren i behandling med DOAK, der får en alvorlig blødning, har en dødelighed på mellem 15-20 % indenfor 30 dage, og dødeligheden er op til ca. 50 % for patienter med intrakranielle blødninger [1]. Den høje dødelighed skyldes patienternes underliggende sygdom, selve blødningen og den øgede risiko for blodpropper som følge af seponering af AK-behandlingen.

Andexanet alfa er rettet mod revertering af effekten af en undergruppe af DOAK, kaldet direkte faktor Xa-hæmmere (FXa-hæmmer), herunder specifikt de to mest anvendte DOAKs i Danmark, rivaroxaban og apixaban [3]. Fagudvalget anslår, at ca. 80.000 patienter aktuelt er i behandling med rivaroxaban og apixaban. Under antagelse af en hændelsesrate for alvorlige blødninger på 2-3,5 % vil 1.600-2.800 patienter årligt få alvorlig direkte FXa-hæmmerassocieret blødning. Heraf vil kun en lille andel have livstruende eller ukontrollerede blødninger og dermed være kandidater til akut reverteringsbehandling. Fagudvalget anslår, at dette gælder for 10 %, svarende til 160-280 patienter årligt. Fagudvalget ønsker at fremhæve, at dette estimat er forbundet med nogen usikkerhed, særligt da estimatet forudsætter, at anvendelsen af andexanet alfa udelukkende forbeholdes den godkendte indikation.

3.2 Andexanet alfa

Andexanet alfa er indiceret til voksne patienter, der behandles med en direkte FXa-hæmmer (apixaban eller rivaroxaban), når der er behov for revertering af lægemidlernes antikoagulerende virkning på grund af livstruende eller ukontrolleret blødning.

Andexanet alfa er en rekombinant modificeret variant af human faktor Xa, som kompetitivt kan binde faktor Xa-hæmmere og dermed ophæve deres hæmmende virkning på faktor Xa. Andexanet alfa er derudover modificeret således, at lægemidlet i modsætning til naturligt FXa ikke kan omdanne protrombin til trombin, da dette ville medføre en stærk protrombotisk effekt. Derudover kan andexanet alfa binde til tissue factor pathway inhibitor (TFPI), hvis funktion er at hæmme de tidlige stadier af koagulationen. Interaktionen mellem andexanet alfa og TPFI samt den kliniske betydning heraf er ufuldstændigt karakteriseret [6]. Det er derfor uklart, om interaktionen mellem andexanet alfa og TFPI kan medvirke til en uønsket protrombotisk effekt [6].

Andexanet alfa kan gives i tillæg til den understøttende behandling, jf. afsnit 4.1, efter et doseringsprogram (tabel 1), der afhænger af dosis af FXa-hæmmeren samt tid siden sidste dosering, idet FXa-hæmmere har halveringstider på 5-12 timer. Ud fra dette bestemmes det, om patienten skal have behandling med en lav eller høj dosis af andexanet alfa. Andexanet alfa gives som en intravenøs bolusinfusion af ca. 30 mg/min.

over 15 minutter (lav dosis) eller 30 minutter (høj dosis) efterfulgt af kontinuert infusion af 4 mg/min. (lav dosis) eller 8 mg/min. (høj dosis) i 2 timer (tabel 2). Hvis dosis af direkte FXa-hæmmer er ukendt, og/eller tid siden sidste dosis er ukendt, gives der som udgangspunkt en høj dosis andexanet alfa (tabel 1). Fagudvalget vurderer, at over halvdelen af patienterne vil blive behandlet med høj dosis andexanet alfa, da det i den akutte situation vil gælde, at enten dosis af FXa-hæmmer eller tid siden sidste dosis vil være ukendt.

Tabel 1. Doseringsprogram for andexanet alfa baseret på sidst anvendte dosis DOAK

DOAK*	DOAK senest administreret dosis	Tidspunkt for sidst administreret DOAK-dosis inden andexanet alfa administreres	
		< 8 timer/ ukendt	≥ 8 timer
Rivaroxaban	≤ 10 mg	Lav dosis	Lav dosis
	> 10 mg /ukendt	Høj dosis	
Apixaban	≤ 5 mg	Lav dosis	
	> 5 mg /ukendt	Høj dosis	
Enoxaparin**	≤ 40 mg	Lav dosis	
	> 40 mg /ukendt	Høj dosis	
Edoxaban**	≤ 30 mg	Lav dosis	
	> 30 mg /ukendt	Høj dosis	
Ukendt	ukendt	Høj dosis	

*Opdateret doseringsprogram jf. protokolændring nr. 4.
** Andexanet alfa er ikke indiceret til patienter behandlet med enoxaparin eller edoxaban, idet der ikke forlægger tilstrækkeligt data for disse.

Tabel 2. Dosering for andexanet alfa

Andexanet alfa dosis	IV initial bolus	IV kontinuerlig infusion
Lav dosis	400 mg initial bolus (30 mg/min)	480 mg kontinuerlig infusion i 120 minutter (4 mg/min)
Høj dosis	800 mg initial bolus (30 mg/min)	960 mg kontinuerlig infusion i 120 minutter (8 mg/min)

Andexanet alfa blev tildelt en betinget markedsføringstilladelse i 2019 under handelsnavnet Ondexxya. EMA har stillet krav om, at der foretages et studie, der kun inkluderer patienter med intrakranielle blødninger.

3.3 Nuværende behandling

Behandling af alvorlig blødning indsættes tidligst muligt og retter sig mod at stoppe blødningen med symptomatisk behandling, samtidig med at kirurgisk kontrol af blødningen søges sikret. Derudover overvejes revertering af den antikoagulerende effekt af pågående AK-behandling. Dette ud fra en individuel vurdering af fordele/risici relateret til blødningens karakter og til indikationen for lægemidlet, idet revertering fjerner den beskyttende antikoagulerende effekt, og derved øges risikoen for blodpropper.

Revertering af AK-behandling kan være specifik eller uspecifik. Til specifik revertering kan anvendes en antidot med direkte neutraliserende effekt på AK-behandlingen, hvis en sådan er tilgængelig. Til uspecifik revertering kan anvendes prohæmostatika (f.eks. tilførsel af koagulationsfaktorer) til hel eller delvis normalisering af koagulationen.

Direkte FXa-hæmmere (i denne kontekst apixaban og rivaroxaban) har ikke tidligere haft en specifik antidot. Den nuværende behandling af alvorlige blødninger associeret med direkte FXa-hæmmere kan bestå af følgende elementer:

- stop behandling med FXa-hæmmer
- foretag relevant laboratorieundersøgelser til udelukkelse af andre årsager til blødning i henhold til DSTH's blødningsapp (DSTH bridging), f.eks. NOAK-TEG, trombocyttal og nyretal
- indled understøttende behandling med blodprodukter og væske
- supplér eventuelt med lægemidler til at hæve blodtrykket, tranexamsyre eller lokal hæmostatika.

Ved synlig blødning foretages kirurgisk kontrol af blødning. Ovenstående punkter kaldes herefter samlet "understøttende behandling". Derudover overvejes uspecifik revertering af den antitrombotiske behandling ved at give protrombinkomplekskoncentrat (PKK) 25-50 IE/kg [7,8], der består af en række forskellige koagulationsfaktorer.

Indikationen for PKK er: "behandling af blødning og perioperativ profylakse af blødning ved erhvervet mangel på vitamin-K-afhængige-koagulationsfaktorer, som f.eks. ved mangel forårsaget af behandling med vitamin K-antagonister (*red. VKA-behandling*) eller i tilfælde af overdosering med vitamin K-antagonister, når der kræves en hurtig korrektion af mangeltilstanden"[9].

PKK er primært tiltænkt revertering af VKA-behandlede patienter, hvor dannelsen af vitamin-K-afhængige -koagulationsfaktorer er hæmmet. Hos patienter behandlet med direkte FXa-hæmmer opstår der en erhvervet funktionel mangel på koagulationsfaktoren Xa (vitamin-K-afhængig-koagulationsfaktor), fordi faktor Xa bindes af FXa-hæmmerne. Dermed vurderer fagudvalget også, at anvendelse af PKK til patienter behandlet med FXa-hæmmere falder indenfor indikationen. Det er vist, at tilførslen af PKK kan genetablere koagulationen hos patienter behandlet med FXa-hæmmere, målt ved at trombindannelsen normaliseres efter indgivelsen af PKK [10]. Anvendelse af PKK ved direkte FXa-hæmmerassocierede blødninger betragtes derfor farmakologisk velbegrundet. Ansøger har tilkendegivet, at de mener, at PKK-behandling til behandling af FXa-hæmmerassocieret blødning er en *off-label*-behandling, men med ovenstående argumenter mener fagudvalget, at PKK udgør standardbehandlingen i Danmark, og at anvendelse af PKK til FXa-hæmmerassocierede blødninger falder indenfor indikationen.

4. Metode

Medicinrådets protokol for vurdering vedrørende andexanet alfa til patienter, som modtager direkte faktor Xa-hæmmer og har livstruende eller ukontrolleret blødning, beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

5.1.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Ansøger har søgt litteratur med søgestrengen fra protokollen. I alt 181 publikationer blev screenet baseret på titel og abstract, og 42 publikationer blev screenet baseret på fuldtekstartikler. Ansøger udvalgte 23 fuldtekstartikler (4 publikationer fra 3 studier med data for andexanet alfa) og 19 artikler med data for PKK. Herudover har ansøger identificeret 4 sammenlignende analyser, hvoraf 3 er upublicerede. Den ene upublicerede analyse indeholder data fra yderligere ét PKK-studie (ORANGE), som Medicinrådet derfor også har inkluderet. Den ene upublicerede analyse (Altevers, 2017) er ekskluderet af Medicinrådet pga. manglende relevans for vurderingen. Fagudvalget har valgt at inkludere de to øvrige upublicerede analyser for at øge datagrundlaget for en sammenligning med PKK. Ansøger oplyser at begge analyser planlægges publiceret i løbet af 2021. Tabel 3 indeholder en oversigt over de identificerede studier.

Tabel 3. Oversigt over inkluderede studier. Grå række indikerer, at studiet ikke indgår i vurderingen. *Data fra studiet indgår i en upubliceret analyse.

Publikationer	Klinisk studie	Population	Intervention	Studieår
Publicerede data				
Connolly, S.J., et al., Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. N Engl J Med, 2016. 375(12): p. 1131-41. Connolly, S.J., et al., Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med, 2019. 380(14): p. 1326-1335.	ANNEXA-4 (NCT02329327)	Patienter behandlet med FXa-hæmmer (apixaban, rivaroxaban, edoxaban eller enoxaparin), som oplevede associeret akut livstruende eller ukontrolleret blødning	Andexanet alfa	2015-2018
Stevens, V.M., et al., Coagulation Factor Xa (Recombinant), Inactivated-Zhzo (Andexanet Alfa) Hemostatic Outcomes and Thrombotic Event Incidence at an Academic Medical Center. Clin Appl Thromb Hemost, 2019. 25: p. 1076029619896619.	Stevens et al.	Patienter behandlet med andexanet alfa	Andexanet alfa	2018-2019
Brown, C.S., et al., Real-world utilization of andexanet alfa. Am J Emerg Med, 2019.	Brown et al. (NCT02329327)	Patienter behandlet med andexanet alfa	Andexanet alfa	2018-2019
Green et al., A three-year prospective study of the presentation and clinical outcomes of major bleeding episodes associated with oral anticoagulant use in the UK (ORANGE study). Haematologica, 2018. 103(4): p. 738-745.	ORANGE*	Patienter i AK-behandling indlagt efter en livstruende eller ukontrolleret blødning	PKK	2013-2016

Publikationer	Klinisk studie	Population	Intervention	Studieår
Gerner, S.T., et al., Association of prothrombin complex concentrate administration and hematoma enlargement in non-vitamin K antagonist oral anticoagulant-related intracerebral hemorrhage. Ann Neurol, 2018. 83(1): p. 186-196.	RETRACE II* (NCT03093233)	Patienter med intrakraniel blødning associeret med behandling med K-vitamin eller orale antikoagulantia	**PKK**	2011-2015
18 andre PKK-studier, se bilag 1 for oversigt	-	-	**PKK**	
Coleman et al., Real-world management of oral factor Xa inhibitor-related bleeds with reversal or replacement agents including andexanet alfa and four-factor prothrombin complex concentrate: a multicenter study Future medicine, 2020.	Coleman et al.	Patienter, som specifikt modtog en Fxa-hæmmer inden indlæggelse, herunder både andexanet alfa og PKK	**Andexanet alfa og PKK**	2016-2019
Ikke-publicerede data				
ANNEXA-4 compared to ORANGE	-	-	**Andexanet alfa og PKK**	-
ANNEXA-4 compared to RETRACE II	-	-	**Andexanet alfa og PKK**	-
Altevers et al., Major and Life-Threatening Bleeds ON Anticoagulation Therapy – Patient Numbers and Outcomes in Germany in 2017.	Altevers et al.	-	-	2016-2017

5.1.2 Gennemgang af studier

ANNEXA-4

ANNEXA-4 var et fase IIIb/IV, prospektivt, ublindet enkeltarmstudie designet til at evaluere effekten og sikkerheden af andexanet alfa som en antidot til Fxa-hæmmere. Studiedeltagere omfattede patienter behandlet med Fxa-hæmmer (apixaban, rivaroxaban, edoxaban eller enoxaparin), som oplevede associeret akut livstruende eller ukontrolleret blødning. Studieårene løb fra 2015-2018. I alt blev 352 voksne patienter inkluderet i ANNEXA-4 til at modtage andexanet alfa (alle inkluderet i *safety*-population). Af disse indgik 254 patienter i evalueringen af effekt. 87 patienter blev ekskluderet fra effektanalysen fordi deres anti-FXa-koncentration var for lav eller manglede. 11 blev ekskluderet, fordi de ikke opfyldte kriterier for blødning.

Der er foretaget et væsentligt antal protokolændringer undervejs i ANNEXA-4-studiet, som kan bidrage til usikkerheder i effektestimaterne. Midtvejs i studiet blev inklusionskriterierne ændret, så flere patienter med intrakraniel blødning blev inkluderet. Patienter med intrakraniel blødning udgør mere end 60 % af studiets population. Studiets to primære endepunkter for effekt var den procentvise ændring i antifaktor Xa-aktivitet og andelen af patienter med fremragende eller god hæmostatisk effekt (vurderet af en uafhængig bedømmelseskomité ud fra præspecificerede kriterier) efter 12 timer. Endepunkter for sikkerhed var dødelighed efter 30 dage (ændret fra oprindeligt 45 dage), trombotiske hændelser og antistofudvikling mod andexanet alfa eller faktor X og Xa.

Fagudvalget noterer sig, at en mindre andel af patienterne modtog behandling med FXa-hæmmer i form af enoxaparin eller edoxaban, og at disse patienter indgår i de samlede

effektestimater for ANNEXA-4, selvom andexanet alfa kun er indiceret til patienter behandlet and apixaban og rivaroxaban. Fagudvalget finder dog, at der er tale om et fåtal af patienter, som ikke forventes at ændre effektestimaterne væsentligt. Udover mangel på en kontrol i studiet er en betydelig begrænsning af ANNEXA-4 de begrænsende inklusions- og eksklusionskriterier, som frasorterede patienter med den dårligste prognose og indebærer risiko for at påvirke overførbarheden af resultaterne til den danske population. Et eksklusionskriterie i ANNEXA-4, som kan have betydning for resultaternes overførbarhed til en dansk population, var 'forventet overlevelse mindre end en måned'. Vurderingen blev foretaget af den behandlende læge ud fra ikke oplyste kriterier. ANNEXA-4 ekskluderede også personer, der havde en *Glasgow coma score* (GCS) < 7, eller patienter der var kandidater til invasiv kirurgi inden for 24 timer (ændret til 12 timer undervejs). Minimalt invasive procedurer som f.eks. bronkoskopi, endoskopi og anlæggelse af centralt venekateter (CVK) var tilladt.

Stevens et al.

Dette studie var et retrospektivt kohortestudie af 13 patienter behandlet med andexanet alfa. Det primære endepunkt var hæmostatisk effektivitet 12 timer efter andexanet alfa-behandling. Tromboemboliske hændelser og 30-dages dødelighed blev også vurderet.

Brown et al.

Retrospektivt studie af serie af kasuistikker (*case series)* af 25 patienter behandlet med andexanet alfa mellem juli 2018 og 29. april 2019 på akademiske centre under Mayo Clinic i USA. Oplysninger om demografi, AK-behandling og reversering samt scanningsbilleder af hjernen blev indsamlet. Studiets primære endepunkter var stabilitet af hæmatom for intrakraniel blødning og hæmostatisk effektivitet for patienter, der gennemgår kirurgiske procedurer. Sekundære endepunkter var tromboemboli og 30-dages dødelighed.

ORANGE

ORANGE var et prospektivt kohortestudie, der indsamlede oplysninger fra britiske hospitaler i årene 2013-2016. Studiedeltagere omfattede patienter i AK-behandling indlagt efter en livstruende eller ukontrolleret blødning. Informationer indsamlet inkluderede patienters baselineegenskaber, type AK-behandling, komorbiditeter og klinisk udfald af behandling efter 30 dage, død eller udskrivning, alt efter hvilken begivenhed der optrådte først. I et understudie af ORANGE, hvor patienterne var i behandling med DOAK, blev der indsamlet oplysninger om komorbiditeter, blødningssteder, hæmatologiske laboratorieresultater, håndtering af blødning og først optrædende event inden for 30 dage (død, udskrivning eller fortsat indlæggelse). Upubliceret data fra studiet er inkluderet i en upubliceret indirekte sammenligning med data fra ANNEXA-4.

RETRACE II

RETRACE var en retrospektiv kohortestudie, der indsamlede oplysninger fra plejecentre i Tyskland i årene 2011-2015. RETRACE II var et opfølgende studie til RETRACE I, der undersøgte en lignende kohorte fra 2006-2010. Studiedeltagere omfattede patienter med intrakraniel blødning associeret med behandling med K-vitamin eller orale antikoagulantia. Endepunkterne omfattede hæmatomforstørrelse, intrakraniel og ekstra-

kraniel komplikation, dødelighed på hospitalet, dødelighed efter tre måneder, volumenændring af intrakraniel blødning, utilstrækkelig hæmostase og modificeret Rankin-skala (mRS). Studiet inkluderer upubliceret data, som indgår i en upubliceret indirekte sammenligning med undergruppen af patienter med intrakraniel blødning fra ANNEXA-4.

Coleman et al.

Dette studie er en retrospektiv undersøgelse af elektroniske patientjournaler fra USA indsamlet mellem januar 2016 og september 2019, hvor blødninger relateret til orale faktor Xa-hæmmere blev behandlet med enten andexanet alfa og PKK. Informationer indsamlet fra patientjournaler inkluderede patientalder ved indlæggelse, køn, blødningstype (gastrointestinalblødning, intrakraniel blødning, kritisk kompartmentblødning (blødning i thorax, underliv, retroperitoneum eller bækken, der ikke kunne behandles med kompression), uspecificeret traumatisk blødning eller andet) længde af hospitalsophold og plejeniveau (indlæggelse versus akutmodtagelse), antikoagulantia administreret før blødning, reverserings- eller genopfyldningsmiddel (f.eks. plasma) og dødelighed på hospitalet.

PKK-studier

For komparatoren PKK har ansøger indsendt 15 retrospektive studier [11–25] og 4 prospektive studier [26–29]. Disse studier havde alle forskellige populationer, stor variation i dosering og forskelle i endepunkter. En oversigt over studierne er præsenteret i bilag 1.

5.1.3 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse beskrevet og herudover præsenteres tilgængelige data for hvert effektmål.

Ansøger har indsendt det datagrundlag, de vurderer, er i bedst mulig overensstemmelse med protokollen. Samlet set vurderer fagudvalget, at datagrundlaget er mangelfuldt, hvad angår sammenligning med en kontrol, herunder den definerede komparator PKK. Alle kliniske studier af andexanet alfa bestod af én studiearm. Det er derfor ikke muligt at foretage nogen direkte sammenligning mellem andexanet alfa og komparator i *head-to-head* kliniske studier. Der foreligger data for andexanet alfa og PKK indhentet retrospektivt fra patientjournaler i Coleman et al. Ansøger har foretaget en indirekte sammenligning ved hjælp af *propensity matched score* af andexanet alfa og PKK på baggrund af upublicerede data fra ORANGE og RETRACE II (sidstnævnte kun for undergruppen med intrakraniel blødning). Der er væsentlige forskelle mellem studiepopulationerne på tværs af studier, og en række af effektmålene er opgjort anderledes end efterspurgt i protokollen. Sammenligneligheden af studierne og tilhørende studiepopulationer er diskuteret i dette afsnit. En oversigt over studiekarakteristikker og tilgængelige data, som er relevant for vurderingen, fremgår af tabel 4. Der er i vurderingen foretaget en deskriptiv gennemgang af tilgængelige data og sammenlignende analyser for hvert effektmål.

Tabel 4. Studiekarakteristikker og tilgængelige data, som er relevant for vurderingen

	ANNEXA-4	ORANGE	RETRACE II	Coleman et al.	PKK-studier (pooled)	Stevens et al.	Brown et al.
Design	fase IIIb/IV, ublindet enkeltarm-studie	Prospektivt kohortestu-die	Retrospek-tivt kohorte-studie	Retrospektiv undersøg-else af patient-journaler	15 retrospek-tive og 4 prospektive observatio-nelle studier	Retrospektiv kohorte-studie	Retrospektiv observation el. case studie
Deltagere	352	2192*	146	1075		13	25
Population (blødningstype)	Alle	Alle	Intrakraniel-le	Alle	Alle	Alle	Alle (+ som forebyg-gende behandling inden operation)
Intervention	Andexanet alfa	PKK	PKK	PKK	PKK	Andexanet alfa	Andexanet alfa
Komparator	-	- (andexanet alfa i upubl. analyse)	- (andexanet alfa i upubl. analyse)	Andexanet alfa	-/andre	-	-
Opfølgningstid (median, min-maks.)	30 dage	30 dage eller indtil udskrivning	3 måneder	Indtil udskrivning	X	30 dage	30 dage
Tilgængelige data							
Dødelighed	√	√	√	√	√	√	√
Komplikationer**	√	-	√	-		-	-
Hæmostase-kontrol***	√	-	-	-	√	√	-
Sikkerheds-aspekter****	√	√	√	√	-	-	-
Livskvalitet	-	-	-	-	-	-	-

* Alle blødninger associeret med warferin eller DOAK. Kun DOAK-associerede blødninger er medtaget i de upublicerede analyser, der inkluderer ORANGE.
** Kun patienter med intrakranielle blødninger.
*** Kun patienter uden intrakranielle blødninger.
**** Sikkerhedsdata er beskrevet med udgangspunkt i EPAR'en for andexanet alfa.

Sammenlignelighed af studier og studiepopulationer

De væsentligste baselinekarakteristika fremgår af tabel 5, og studiernes sammenlignelighed er beskrevet herunder.

ANNEXA-4 og ORANGE, upubliceret indirekte analyse

I ANNEXA-4 var der mange eksklusionskriterier vedrørende patienternes forventede prognose, blødningens karakter, tidligere trombotiske events m.m. ANNEXA-4 inkluderede derfor en snævrere population end ORANGE, som omfattede patienter i behandling med et oralt antikoagulant, og som oplevede en livstruende eller ukontrolleret blødning. Fagudvalget vurderer, at patienterne, der indgår i ORANGE, er mere repræsentative for patienter i dansk klinisk praksis sammenlignet med studiepopulationen i ANNEXA-4. De forskellige kriterier i de to studier påvirker studiernes sammenlignelighed, og fagudvalget vurderer, at patientpopulationernes prognose kan have været forskellige, hvilket kan påvirke effektestimaterne for især 30-dages dødelighed. Patienter, der oprindeligt blev betragtet som kandidater til operation, vil f.eks. have en dårligere prognose. En markant

andel af patienter i ANNEXA-4 har intrakraniel blødning, hvilket også begrænser sammenligneligheden af populationerne.

ANNEXA-4 og RETRACE II, upubliceret indirekte analyse

Den indirekte sammenligning af ANNEXA-4 og RETRACE II er foretaget for undergruppen af patienter med intrakranielle blødninger, da studiepopulationerne i RETRACE II udelukkende består af disse. ANNEXA-4 inkluderede hovedsageligt patienter behandlet med apixaban eller rivaroxaban og ekskluderede patienter med tremor eller trauma. Disse selektionskriterier indgik ikke i RETRACE II, hvor patienterne blev ekskluderet, hvis det var mere end 18 timer siden, de havde taget deres DOAK-behandling, hvis de havde en GCS < 7, et intrakranielblødningsvolumen på mere end 60 ml ved baseline eller hvis de havde et alkoholmisbrug eller unormal leverfunktion. Eksklusionskriteriet 'forventet overlevelse mindre end en måned' i ANNEXA-4 bidrager også her til usikkerhed i den sammenlignende analyse.

Coleman et al.

Coleman et al. er et registerstudie, og derfor er de patienter, hvis informationer indgår i studiet, ikke underlagt samme selektion som patienter i ANNEXA-4 pga. et retrospektivt observationelt studiedesign. Patienter, der modtog behandling med andexanet alfa og patienter, der modtog PKK, forventes derfor at være bedre balanceret ift. baseline-karakteristikker, hvilket styrker overførbarheden af resultater til dansk klinisk praksis. Bl.a. udgør andelen af patienter med intrakranielle blødninger kun omkring 20 % i modsætning til omkring 70 % i ANNEXA-4.

Individuelle PKK-studier

Studierne med data for PKK-behandling varierer i deres inklusions- og eksklusions-kriterier. Dette betyder, at de inkluderede patienter har forskellig prognose ift. de relevante effektmål, og en sammenligning af resultater på tværs af studierne vil ikke være retvisende. Det er ikke muligt at vurdere, hvor meget forskellene i patientpopulationerne indvirker på effektestimaterne. En formel sammenligning af PKK-studiepopulationerne er derfor ikke foretaget, og data er beskrevet for hvert studie, hvor det er relevant.

Tabel 5. Population- og baselinekarakteristikker

	ANNEXA-4 (Conolly 2019)		ORANGE (Green 2018)	RETRACE II* (Gerner 2018)		Coleman et al. 2020	
	***Safety* population n = 352**	***Efficacy* population n = 254**	**N i alt = 2192 n = 372 (rivaroxaban n = 283, apixaban n = 89)**	**Forstørrelse af hæmatom n = 49**	**Ingen forstørrelse af hæma-tom = 97**	**Andexanet alfa n = 342**	**4F-PKK n = 733**
Alder, år (IQR), (SD)	77,4 ± 10.8	77,1 ± 11.1	R: 82 [74-88] A: 81 [76-86]	76,6 (7,3)	77,9 (7,9)	69,1	70,1
Køn, mænd, n (%)	187 (53)	129 (51)	R: 153 (54) A: 35 (39)	31 (63)	46 (47)	188 (55 %)	369 (50 %)
Etnicitet Kaukasisk, n (%)	307 (87)	222 (87)	NA	NA	NA	NA	NA
Blødningstype n (%)							
Intrakraniel	227 (64)	171 (67)	R: 11 (4) A: 4 (4)	49 (100)	97 (100)	20 %	23 %
Gastrointestinal	90 (26)	62 (24)	R: 10 (4) A: 4 (4)	NA	NA	40 %	41 %
Anden	35 (10)	21 (8)	R: 6(2) A: 0	NA	NA	40 %	36 %
Ukendt			R: 73 (26) A: 28 (31)				
AK-behandling, n (%)							
Rivaroxaban	128 (36)	100 (39)	283 (13)	110 (75)		50 %	41 %
Apixaban	194 (55)	134 (53)	89 (4)	21 (14)		47 %	51 %
Enoxaparin	20 (6)	16 (6)	NA	NA		NA	NA
Edoxaban	10 (3)	4 (2)	NA	NA		3 %	8 %

*Pt. med DOAK-relaterede intrakranielle blødninger med follow-up imaging, n = 146

5.1.4 Evidensens kvalitet

Da der er tale om etarmede studier, har Medicinrådet ikke anvendt GRADE til at foretage en systematisk vurdering af evidensens kvalitet. Kvaliteten af evidensen, som danner baggrund for vurderingen, er meget lav, når det er naive sammenligninger af studiearme fra forskellige studier. Evidensens kvalitet i de indirekte sammenligninger af andexanet alfa og PKK afhænger at studiepopulationernes sammenlignelighed (beskrevet i afsnit 5.1.2.) og kvaliteten af de foretagne analyser. Nedenfor følger en beskrivelse af de forhold, der påvirker kvaliteten af de udførte sammenlignende analyser mellem data for andexanet alfa fra ANNEXA-4 og data for PKK fra patientkohorterne i ORANGE og RETRACE.

Propensity score matching er en statistisk metode, der bruges til at matche individer i to patientkohorter. ANNEXA-4-studiepopulationen sammenlignes med *propensity score*-matchede data fra hhv. ORANGE og RETRACE II på baggrund af kriterier, som anses at være vigtige for at sikre sammenligneligheden.

Pålideligheden af resultaterne er især afhængig af succesen af matching mellem patienter/populationer i de sammenlignende studier, hvor især prognostiske variable bør indgå

som matching-kriterier. Antallet af matching-kriterier kan også påvirke resultatet af analysen. Patienter i ANNEXA-4 adskilte sig væsentligt fra patienter i ORANGE ift. blødningstype og adskilte sig fra både patienter I ORANGE og RETRACE II på baggrund af forskellige inklusions- og eksklusionskriterier, som har betydning for patienternes prognostiske udgangspunkt. Der er ikke er matchet på eksklusionskriterierne fra ANNEXA-4, hvilket kan betyde, at patienter med den dårligste prognose ikke indgår i datagrundlaget fra ANNEXA-4, mens de vil indgå i grundlaget fra ORANGE. Sammenligningerne vurderes samlet set forbundet med væsentlig usikkerhed, idet der er store forskelle i de inkluderede populationer pga. eksklusionskriterier og udeladelse eller fravær af data for adskillige væsentlige kovariater/prognostiske faktorer. Populationernes størrelse begrænser, hvor mange kovariater som kan indgå i analysen, da det er sværere at finde par (en matching), jo flere variable der inddrages. Fagudvalget vurderer derfor, at det er vanskeligt at sikre, at de opnåede effektestimater i *propensity score-analyserne* er repræsentative for den forventede effekt i den danske patientpopulation.

5.1.5 Effektestimater og kategorier

På grund af de begrænsninger, der er beskrevet vedrørende studiernes design og sammenlignelighed, kan der ikke foretages en formel kategorisering af den kliniske værdi af andexanet alfa sammenlignet med nuværende klinisk praksis i henhold til Medicinrådets metoder. Vurderingen vil derfor basere sig på en deskriptiv gennemgang af det tilgængelige data. For hvert effektmål er de relevante effektestimater fra de inkluderede studier beskrevet. Hvor det er muligt, er data opgjort separat for patienter med intrakranielle blødninger og andre typer blødninger.

Dødelighed

Som beskrevet i protokollen er effektmålet *dødelighed* kritisk for vurderingen af lægemidlets værdi for patienterne. Effektmålet *dødelighed* opgives forskelligt på tværs af studier og analyser. I ANNEXA-4, Stevens et al., Brown et al. og ORANGE er effektmålet rapporteret som 30-dages dødelighed, mens det i Coleman et al. og RETRACE II er rapporteret som dødelighed under indlæggelse. For individuelle PKK-studier er dødelighed opgjort forskelligt. Resultater for andexanet alfa fremgår af tabel 6.

Dødelighed 30 dage efter behandling med andexanet alfa for alle blødningstyper er rapporteret i fire studier og varierede fra 14 % til 24 %.

Tabel 6. Effektestimater for 30-dages dødelighed ved behandling med andexanet alfa

Studie	Andexanet alfa-behandling	N	Effektestimater for 30-dages dødelighed			
			Alle blødninger	Intrakranielle	Gastro-intestinale	Andre
ANNEXA-4 Conolly et al., 2016	Høj dosisi: 11 % (5/47) Lav dosis: 89 % (42/47)*	67	15 %	21 % (6/28)	6 % (2/33)	-
ANNEXA-4 Conolly et al., 2019	(Som angivet i tabel 1)	352	14 %	-	-	-
Brown et al., 2019	Høj dosis: 27 % (6/22) Lav dosis: 73 %	22	24 %	23 % (3/13)	25 % (1/4)	33 % (2/6)
Stevens et al., 2019	Høj dosis: 15 % Lav dosis: 85 %	13	15 %	33 % (2/6)	-	-

*Defineret for *efficacy* population, (doseringsprogram som beskrevet i tabel 1); **_safety_ population.

Den laveste dødelighed blev rapporteret i ANNEXA-4. Dødelighed ved intrakraniel blødning blev rapporteret i tre studier og varierede fra 21 % til 33 %. Dødelighed efter gastrointestinale blødninger blev rapporteret i to studier og var hhv. 6 % og 25 %.

På grund af stor heterogenitet mellem PKK-studierne og forskelle i inklusions- og eksklusionskriterier er det ikke muligt at kombinere data på en meningsfuld måde. Der var forskelle i PKK-dosis og mængden af FXa, der tidligere var blevet administreret. Alle fire andexanet alfa-studier rapporterede dødelighed efter 30 dage, mens tidspunktet for opgørelsen af dødelighed varierede i PKK-studierne mellem 30 dages dødelighed, død inden for 1-3 dage, dødelighed under indlæggelse og nogle rapporterede dødelighed uden fast tidspunkt. Effektestimaterne fra tre PKK-studier, der som andexanet alfa-studierne rapporterede 30-dages dødelighed, viste varierende estimater fra 23,1 % til 44 % (tabel 7) [26,30,31].

Tabel 7. Effektestimater for 30-dages dødelighed ved behandling med PKK

Studie	PKK-behandling	N	Effektestimater for 30-dages dødelighed	
			Alle blødninger	Intrakranielle
Arachchillage et al. (2019) [30]	PKK 16,7-50 U/kg (rivaroxaban; gns. 26,8) og 18,5-43 U/kg (apixaban; gns. 25)	80*	33 % Apixaban: 33,5 % Rivaroxaban: 32,5 %	Apixaban: 38,1 % Rivaroxaban: 44 %
Mejeed et al. (2017) [26]	PKK mediandosis 2000 IU (1500-2000) Apixaban 26,7 U/kg (22,0-29,9) Rivaroxaban 26,7 U/kg (20,8-29,4)	84	32 %	33,9 %
Schenk et al. (2018) [31]	PKK 25 U/kg	13	23,1 %	

*40 behandlet med apixaban og 40 med rivaroxaban.

Resultater fra de øvrige PKK-studier, der opgjorde dødelighed efter andre tidspunkter, fremgår af bilag 3. Dødeligheden under indlæggelse var generelt lavere og spændte fra 9,5 % til 33 % [11,13,15,19,20,22–24,28,32]. De resterende studier, som rapporterede

dødsfald inden for 1-3 dage og dødsfald inden for en ukendt tidsramme, varierede mellem 2,3 % og 20 % [12,16,29].

I studiet af Coleman fra 2019 er dødelighed under indlæggelse hos patienter behandlet med henholdsvis andexanet alfa og PKK opgjort. Resultaterne fremgår af tabel 8.

Tabel 8. Effektestimater for dødelighed under indlæggelse, Coleman et al.

Dødelighed under indlæggelse	Andexanet alfa N = 342		PKK* N = 733	
	%	antal events/pt. analyseret	%	antal events/pt. analyseret
Alle typer blødninger	4	12/342	10	74/733
Intrakraniel	9	6/67	25	12/303
Gastrointestinal	1	2/137	4	43/170
I kritisk område	0	0/11	4	1/26
Trauma	4	4/105	7	16/214
Andre	0	0/22	10	2/20

*4F-PKK.

Ansøger har indsendt en upubliceret *propensity score*-matchet analyse, hvor resultaterne fra ANNEXA-4 og ORANGE er sammenlignet for alle blødningstyper, intrakranielle, gastrointestinale og andre blødninger (tabel 9). *Propensity score*-matching var muligt for følgende variable: alder, blødningstype samt tidligere medicinsk sygehistore med koronararteriesygdom, slagtilfælde, forbigående iskæmisk anfald, dyb venetrombose, venøs tromboembolisk sygdom, atrieflimren, hypertension, diabetes, nedsat nyrefunktion og kræftsygdom (se bilag 2). Ud af 145 patienter behandlet med PKK fra ORANGE var der [redacted] tilbage efter matchingen med de 322 patienter fra ANNEXA-4. Den lille andel af patienter i ORANGE, der kunne matches til patienter i ANNEXA-4, bidrager med usikkerhed til analysen.

Tabel 9. Effektestimater (propensity score-matchede) for 30-dages dødelighed (justeret), ANNEXA-4 vs. ORANGE

Population	Studier i analysen	Antal matches N	Justeret 30-dages dødelighed for PKK, % [CI95 %]	Justeret 30-dages dødelighed for andexanet alfa [CI 95 %]
[redacted]				

Ansøger har indsendt en tilsvarende analyse, der sammenligner dødeligheden efter 30 dage hos patienter behandlet med andexanet alfa fra ANNEXA-4 og patienter behandlet med PKK fra RETRACE II. Patienterne blev matchet på flere kovariater afhængigt af effektmålet. Effektestimaterne for 30-dages dødelighed fra de enkelte studier fremgår af tabel 10, mens de propensity-matchede effektestimater fremgår af tabel 11.

Tabel 10. Effektestimater (umatchede) for 30-dages dødelighed, ANNEXA-4 og RETRACE II

Behandling	Studier i analysen	N	Effektestimater	Bemærkning
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 11. Effektestimater (propensity-score-matchede) for 30-dages dødelighed, ANNEXA-4 vs. RETRACE II.

Effektmål	Studier i analysen	Kovariater/ matchede variable	Andexanet alfa N	PKK N	Hazard ratio [CI95 %], p-værdi
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

På tværs af de forskellige studier og sammenligninger ser det ud til at behandling med andexanet alfa giver en lavere dødelighed end behandling med PKK. Fagudvalget bemærker dog, at der væsentlige forskelle mellem studierne og svagheder ved de udførte analyser som vanskeliggør vurderingen. Særligt fremhæver fagudvalget studiepopulationernes forskellighed og studiernes design, som det er vanskeligt at kompensere for i de udførte analyser. Fagudvalget finder det derfor ikke muligt at drage konklusioner på forskelle mellem de to behandlinger, hvad angår effektmålet dødelighed.

Komplikationer - funktionsnedsættelse hos patienter med intrakranielle blødninger

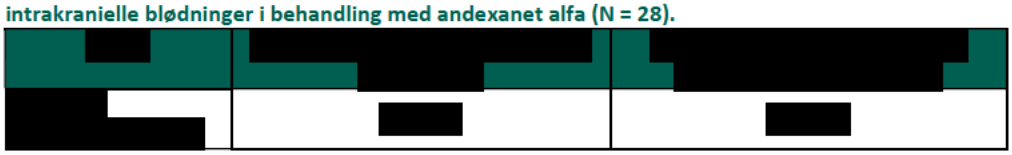
Fagudvalget har inkluderet effektmålet komplikationer i form af funktionsnedsættelse hos patienter med intrakraniel blødning som et kritisk effektmål i vurderingen. Effektmålet er opgjort med værktøjet modificeret rankinskala (mRS), som er det mest anvendte kliniske effektmål i kliniske forsøg med patienter, der har lidt neurologisk skade [33]. mRS måler graden af funktionsnedsættelse samt evnen til at udføre daglige aktiviteter for patienter, der har lidt en neurologisk skade. mRS går fra: 0 (ingen symptomer), 1 (ingen signifikant funktionsnedsættelse), 2 (svag funktionsnedsættelse), 3 (moderat funktionsnedsættelse), 4 (moderat til svær funktionsnedsættelse), 5 (svær funktionsnedsættelse) til 6 (død). Fagudvalget ønskede at belyse effektmålet som andelen af patienter, der opnår et "godt helbredsstadie" (mRS-score på 0-2) 30 dage efter opstart af behandling. Øvrige scores mellem 3 og 6 betragtes som "uønskede helbredsstadier".

Data fra ANNEXA-4 fremgår af tabel 12. Her er data opgjort som et gennemsnit før og efter behandling med andexanet alfa. Fagudvalget bemærker, at en funktionsscore på omkring 2 ved baseline er god og vidner om, at de patienter, der overlever i ANNEXA-4,

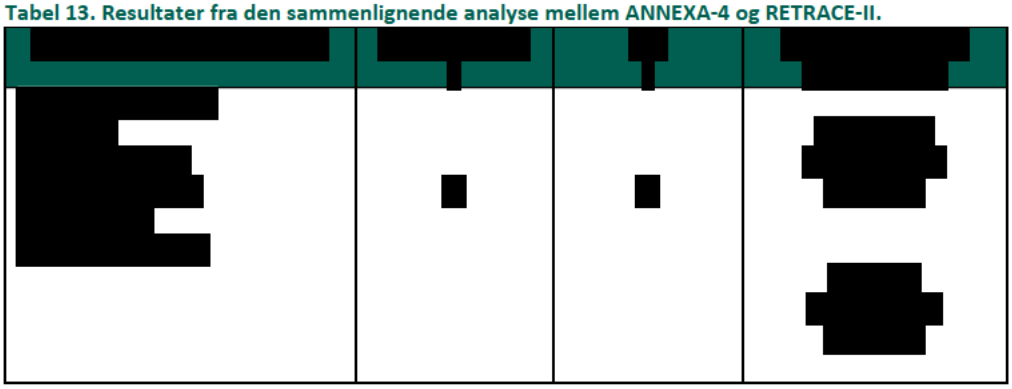
har et funktionsniveau, som ikke er meget påvirket af deres intrakranielle blødning. Det indikerer, at blødningerne ikke har været alvorlige og bekræfter, at patientpopulationen i studiet er en selekteret population med god prognose.

Ansøger har også indsendt en sammenlignende *propensity score*-matched-analyse mellem patienter behandlet med andexanet alfa fra ANNEXA-4 og patienter behandlet med PKK fra RETRACE-II (tabel 13). Her er ikke oplysninger om patienternes udgangs-niveau.

Tabel 12. Modified Rankin Scale ved baseline og efter 30 dage hos overlevende patienter i med intrakranielle blødninger i behandling med andexanet alfa (N = 28).



Tabel 13. Resultater fra den sammenlignende analyse mellem ANNEXA-4 og RETRACE-II.



De øvrige studier rapporterer ikke data for dette effektmål. Fagudvalget vurderer, at der på baggrund af det foreliggende data ikke er grundlag for at udtale sig om, hvorvidt der er forskel på effekten på funktionsniveauet mellem behandling med andexanet alfa og behandling med PKK.

Hæmostasekontrol hos patienter uden intrakranielle blødninger

Som beskrevet i protokollen er effektmålet *hæmostasekontrol* vigtig for vurderingen af lægemidlets værdi for patienter uden intrakranielle blødninger, fordi det afdækker den farmakologiske effekt af lægemidlet og forventes at korrelere med behovet for under-støttende behandling. Effektmålet er, når det måles med biokemiske markører, mindre relevant for patienter med intrakranielle blødninger. Konsekvenserne af intrakranielle blødninger er oftere svære at påvirke ved øget hæmostasekontrol, da selv små hæmatomer kan forårsage store skader i hjernen.

Hæmostasekontrol inden for 12 timer blev rapporteret i tre publikationer med andexanet alfa [34–36]. Hæmostasekontrol blev målt i overensstemmelse med International Society on Thrombosis and Haemostasis (ISTH) nye standardkriterier. Hæmostasekontrol blev vurderet på baggrund af hæmoglobinniveauer og hæmatokrit-værdier efter 12 timer. Fald på maksimum 20 % i forhold til baseline med mindre end to

supplerende koagulationsinterventioner (f.eks. plasma eller PKK) blev vurderet at være god hæmostase. I ANNEXA-4 blev klinisk hæmostase bedømt som 'fremragende' eller 'god' hos 79-82 % af patienterne 12 timer efter andexanet alfa-infusion [34,35]. Ca. 85 % af patienterne opnåede hæmostasekontrol i det øvrige studie [36]. Detaljer og effekt-estimater fremgår af tabel 14.

Tabel 14. Oversigt over studier, der rapporterer hæmostasekontrol (ikke pt. med intrakranielle blødninger) samt tilhørende effektestimater.

Studie	Andenexanet alfa-behandling	N	Effektestimater, andel med hæmostasekontrol % [CI 95 %]	
Connolly 2016	ANNEXA-4, Høj dosis: 11 % (5/47) Lav dosis 89 % (42/47)	47 Gastrointestinal: 27 Intrakraniel: 20	**Overordnet:** Lav dosis: Høj dosis: Rivaroxaban: Apixaban: Gatrointestinal:	**79 % [64-89]** 76 % [61-88] 100 % [48-100] 81 % [61-93] 75 % [51-91] 84 % [64-96]
Connolly 2019	ANNEXA-4 (doseringsskema som 3.2)	249 Gastrointestinal: 62 Andre: 21	**Overordnet:** Lav dosis: Høj dosis: Rivaroxaban: Apixaban: Gastrointestinal: Andre:	**82 % [77-87]** 83 % [78-88] 78 % [65-91] 80 % [72-88] 83 % [77-90] 85 % [68-96] 86 % [74-86]
Stevens 2019	Høj dosis: 15% Lav dosis: 85 %	7 uden intrakranielle blødninger (13 i alt)	Overordnet: Non-ICH:	77 % (10/13) 86 % (6/7)

Hæmostasekontrol blev rapporteret i 15 PKK-studier, hvor hovedparten imidlertid ikke anvendte ISTH-definitionen. Af samme grund er tolkningen af resultaterne for hæmo-stasekontrol behæftet med store usikkerheder.

Et enkelt studie rapporterede hæmostaseeffektivitet inden for 48 timer [30], fem studier inden for 24 timer og otte rapporterede slet ikke en tidsramme. I Arachchillage et al. 2019 [30] blev hæmostasekontrol vurderet efter, om der var tilbagevendende blødning, og om patienten stadig var i live. Hæmostasekontrol blev opnået for ca. 74 % af patienterne inden for 48 timer. Fem studier målte effekt inden for 24 timer, hvor hæmostaseeffektivitet lå inden for et interval på 65-87,5 % [7,26,28,37,38]. I fem studier, hvor tidsrammen ikke blev rapporteret, blev hæmostaseeffektivitet estimeret til at ligge inden for et interval på 66-94,4 % [12,13,15,16,31].

Overordnet set opnåede mellem 65-88 % af patienter behandlet med PKK hæmostase-kontrol (defineret ud fra forskellige kriterier) inden for 24-48 timer eller 66-94 % inden

for en ikkerapporteret tidsramme. Til sammenligning opnåede mellem 79-86 % af patienter behandlet med andexanet alfa hæmostasekontrol inden for 12 timer (defineret ud fra ISTH-kriterier). Der er et væsentligt overlap mellem andele, der opnår hæmostase-kontrol efter behandling med hhv. PKK og andexanet alfa. Fagudvalget er ikke i stand til at vurdere, om der er en klinisk betydende effektforskel mellem de to behandlinger, men finder at der generelt opnås god hæmostasekontrol med både PKK og andexanet alfa.

Bivirkningsprofil og sikkerhedsaspekter

Effektmålet *bivirkningsprofil* og *sikkerhedsaspekter* er vigtig for vurderingen af lægemid-lets værdi for patienterne, fordi der er tale om en akut livstruende eller invaliderende situation. Sikkerheden af behandling vurderes ifølge protokollen ud fra en kvalitativ gennemgang af uønskede hændelser og bivirkninger, herunder særligt alvorlige uønske-de hændelser. Da der ikke findes sammenlignende data for sikkerhed, gennemgås evidensen for andexanet alfa og PKK enkeltvis.

Sikkerhed ved behandling med andexanet alfa

Sikkerheden af behandling med andexanet alfa evalueres ud fra en *safety*-population, som bestod af 247 raske forsøgspersoner, som fik administreret en FXa-hæmmer såvel som hos 352 patienter i ANNEXA-4. Alle informationer, der vedrører sikkerheden af andexanet alfa, er gengivet fra EPAR'en.

I de kliniske forsøg med raske forsøgspersoner blev der ikke rapporteret om alvorlige bivirkninger. De hyppigst observerede bivirkninger var milde eller moderate infusions-relaterede reaktioner, som optrådte hos flere kvinder end mænd. Af særlig interesse blev der rapporteret dosisafhængige forhøjelser i koagulationsmarkører (TAT, D-dimer og protrombinfragmenter F1+2), der varede mellem flere timer og et par dage efter administration. Der blev ikke rapporteret om trombotiske hændelser.

I ANNEXA-4 oplevede én (0,3 %) patient en alvorlig eller svær infusionsrelateret reaktion. Seksogtredive af 352 (10,3 %) patienter med 30-dages opfølgningsdata havde tromboemboliske hændelser, herunder venøs tromboemboli, hjerteinfarkt og slagtilfælde. Koagulationsmarkører blev ikke målt i ANNEXA-4, som det var tilfældet i de kliniske forsøg med raske forsøgspersoner. Ti af 36 (27, 8 %) patienter, som tidligere var i behandling for venøs tromboemboli og/eller atrieflimren, havde genstartet antitrombotisk behandling på tidspunktet for hændelsen. Fagudvalget finder, at frekvensen af trombotiske hændelser efter behandling med andexanet alfa er bekymrende høj og udgør den største sikkerhedsrisiko ud fra det forelæggende datagrundlag.

Ifølge EPAR'en er sikkerheden ikke blevet evalueret hos patienter, der fik PKK, rekombinant faktor VIIa eller fuldblod inden for syv dage inden blødningshændelsen, da disse blev ekskluderet fra ANNEXA-4. Understøttende behandling med PKK, rekombinant faktor VIIa eller fuldblod bør derfor undgås, da mulige krydseffekter med andexanet alfa ikke er undersøgt.

Sikkerhed ved behandling med PKK
Fagudvalget beskriver på baggrund af kliniske erfaring, at PKK-behandling generelt er veltolereret og, at den primære bekymring som ved andre behandlinger for akut blødning er risikoen for tromboser.

Livskvalitet
Som beskrevet i protokollen er effektmålet livskvalitet vigtig for vurderingen af lægemidlets værdi for patienterne. Ansøger har ikke indsendt data for effektmålet, og det kan derfor ikke vurderes, om andexanet alfa har betydning patienternes livskvalitet.

5.1.6 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af andexanet alfa sammenlignet med PKK til patienter med livstruende eller ukontrolleret blødning ikke kan kategoriseres i henhold til Medicinrådets metoder. Datagrundlaget består af ukontrollerede studier med forskellige populationer og designs og vurderes samlet set af meget lav evidenskvalitet.

Fagudvalget bemærker at, effekterne af komparatoren PKK trods sin almindelige anvendelse til patienter med livstruende eller ukontrolleret blødning ikke er tilstrækkeligt dokumenteret i det foreliggende datagrundlag.

På baggrund af de foreliggende data ser det ud til, at andexanet alfa har god effekt på det kritiske effektmål *dødelighed* i en selekteret patientpopulation med en i forvejen relativt god prognose. Det foreliggende datagrundlag for hæmostasekontrol og komplikationer ved intrakranielle blødninger giver ikke anledning til at skelne mellem effekten af andexanet alfa og PKK. Der er ikke data for det vigtige effektmål *livskvalitet*.

Fagudvalget bemærker at EPAR'en beskriver en uønsket potentiel protrombotisk effekt af andexanet alfa, men dette er endnu ikke tilstrækkeligt belyst.

Fagudvalget bemærker endvidere, at det kliniske set-up er er en vigtig parameter ved behandling af akutte blødninger generelt og særligt ved anvendelse af andexanet alfa. Herunder et tilstrækkeligt patientvolumen, der tillader ekspertise og praktisk erfaring med denne patienttype (herunder f.eks. tilgang til højt specialiseret blødningsrådgivning og kirurgisk ekspertise). Dette set-up er vurderet essentielt for resultatet af den medicinske behandling.

Fagudvalget udtrykker bekymring for, at andexanet alfa i praksis vil blive brugt til ikke godkendte indikationer og for den udfordrende praktiske håndtering af lægemidlet.

Samlet set vurderer fagudvalget, at det ud fra det foreliggende datagrundlag ikke er muligt at vurdere, om andexanet alfa sammenlignet med komparatoren PKK er et bedre, dårligere eller ligeværdigt behandlingsalternativ.

6. Andre overvejelser

6.1 Mulig protrombotiske effekt af andexanet alfa

Andexanet alfa er en analog til naturligt FXa, men molekylestruktur er designet med henblik på at minimere protrombotisk aktivitet. Blandt andet kan andexanet alfa ikke kløve prothrombin til thrombin, fordi det aktive site for den enzymaktivitet er modificeret. Andexanet alfa interagerer med den naturlige FXa-hæmmer, TFPI med samme affinitet som naturligt FXa og binder til kunstige FXa-hæmmere med høj affinitet. Herved kan der være en protrombotisk effekt af andexanet alfa. I ANNEXA-4 blev patienterne monitoreret for trombotiske events. Af de 352 patienter i safety-populationen rapporterede 34 (9,7 %) trombotiske events, og hos 10 af de patienter vurderede investigator, at de trombotiske events var relateret til behandling med andexanet alfa.

Af EPAR'en fremgår, at der er identificeret en risiko for tromboemboliske events i forbindelse med behandling med andexanet alfa. Risikoen kan involvere patienter behandlet med høj dosis og patienter på lavdosis antiokoagulerende behandling. Der mangler information fra en kontrolpopulation, der ikke behandles med andexanet alfa.

6.2 Rekruttering af patienter med intrakranielle blødninger

Protokolændringen til at inkludere flere patienter med intrakranielle blødninger og på den måde berige patientpopulationen med ICH-patienter skete ifølge ansøger på baggrund af et ønske om, at studiepopulationen skulle afspejle en patientpopulation med højeste potentielle mortalitet og behandlingsgevinst ved behandling med andexanet alfa. In- og eksklusionskriterierne blev bestemt med involvering af EMA, og ansøger beskriver, at man har forsøgt at ramme en bred indikation ved blandt andet at have få eksklusionskriterier for samtidig medicinsk behandling (kun behandling med præparater der påvirkede koagulationsprocessen). Der findes ikke et standardiseret anvendeligt FXa-aktivitets assay, som ellers kunne være anvendt til at in- og ekskludere patienter. De maksimum 18 timer siden DOAK-behandling blev indskrevet for at sikre tilbageværende FXa-hæmmer aktivitet hos de inkluderede patienter. Det igangværende studie, der kun inkluderer ICH-patienter, er krav fra EMA i forbindelse med markedsføringstilladelsen.

6.3 Dødelighed hos patienter med intrakranielle blødninger og andre type blødninger

Resultaterne er opgjort i de forskellige subgrupper i det omfang, det var muligt. Fagudvalget finder ikke anledning til at skelne mellem effekten af andexanet alfa i de forskellige subgrupper.

6.4 Virkningsvarigheden

Andexanet alfa doseres som en bolus efterfulgt af infusion i 2 timer. Ansøger angiver i deres endelige ansøgning, at effekten varede ved i 1-2 timer herefter. Ved fortsat behov skal behandlingen derfor gentages efter ca. 4 timer.

6.5 Risiko for indikationsskred

Fagudvalget vurderer, at der er risiko for indikationsskred ved behandling med andexanet alfa, da det akutte setting ofte ikke tillader en vurderingen af om en given patient er omfattet af indikationen og hvilket doseringsprogram, der bør følges.

Andexanet alfa vil med stor sandsynlighed også blive anvendt til patienter, der er behandlet med edoxaban og lavmolekylære hepariner, hvilket er uden for indikation. Fagudvalget fremhæver også risiko for anvendelse som forbehandling inden akut kirurgi, selvom det er angivet som et forhold under produktresumeets afsnit 4.4 *Særlige advarsler og forsigtighedsregler vedrørende brugen*. Andexanet alfa vil ofte i praksis blive anvendt i den høje dosis og til flere patienter, end de der er behandlet med rivaroxaban og apixaban.

6.6 Praktisk håndtering af andexanet alfa

Ansøger har gjort rede for den praktiske håndtering af andexanet alfa i den endelige ansøgning, som også er beskrevet i produktresuméet [9]. Fagudvalget vurderer, at håndteringen kan skabe udfordringer i det akutte setting og fremhæver særligt fremstillingen af den opløsning, der skal gives til patienten, som skal foregå sterilt, og hvor der skal anvendes et stort væskevolumen, der kræver anvendelse af flere sprøjter a 20 og 60 mL eller større.

Andexanet alfa er formuleret i 20 mL-vials som pulver, der skal opløses i vand til injektion (200 mg pr. vial). For hvert vial skal der anvendes 20 mL vand til injektion for at opnå en koncentration på 10 mg/mL.

Ved opløsning af andexanet alfa skal man undgå at ryste vialet, da det kan få væsken til at skumme. Det tager 3-5 minutter for pulveret at opløses i væsken, hvorefter det skal inspiceres for partikler og misfarvning.

Bolusinfusionen (2-4 hætteglas) og infusionerne (3-6 hætteglas) skal fremstilles separat, før det overføres til IV-poser. Før administration ved i.v.- infusion skal et 0,2 eller 0,22 mikron in-line polyethersulfon (PES) eller tilsvarende lavproteinbindende filter anvendes.

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende behandling og forebyggelse af venøse blodpropper hos kræftpatienter

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Jesper Kjærgaard *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Anders Krog Vistisen *Afdelingslæge*	Region Nordjylland
Kan ikke udpege	Region Midtjylland
Lennart Friis-Hansen *Overlæge*	Region Syddanmark
Jytte Jensen *Overlæge*	Region Sjælland
Jesper Kjærgaard *Overlæge*	Region Hovedstaden
Christina Ruhlmann *Afdelingslæge*	Dansk Selskab for Klinisk Onkologi
Maja Hellfritzsch Poulsen *Læge*	Dansk Selskab for Klinisk Farmakologi
Eva Leinø *Overlæge*	Dansk Hæmatologisk Selskab
Dorte Gijsbrechts Husum *Overlæge*	Dansk Cardiologisk Selskab
Anne-Mette Hvas *Professor, overlæge*	Dansk Selskab for Klinisk Biokemi
Morten Schnack Rasmussen *Overlæge*	Dansk Selskab for Trombose og Hæmostase

Sammensætning af fagudvalg	
Merete Schmiegelow *Patient/patientrepræsentant*	Danske Patienter
Lennart Jønsson *Patient/patientrepræsentant*	Danske Patienter

Medicinrådets sekretariat

Medicinrådet
Dampfærgevej 27-29, 3.th.
2100 København Ø
+45 70 10 36 00
medicinraadet@medicinraadet.dk

10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	28. april 2021	Godkendt af Medicinrådet

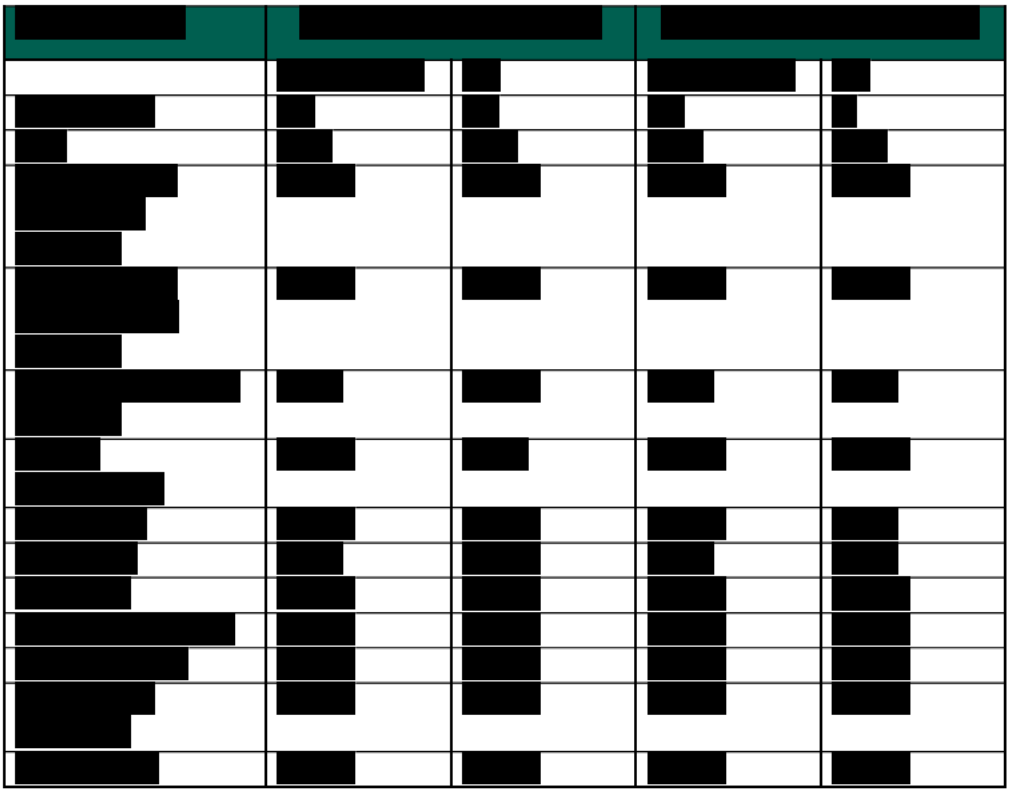
11. Bilag

Bilag 1: Oversigt over inkluderede PKK-studier

Publikation	Studieperiode	Ref
Arachchillage, D.R.J., et al., Efficacy and safety of prothrombin complex concentrate in patients treated with rivaroxaban or apixaban compared to warfarin presenting with major bleeding. Br J Haematol, 2019. 184(5): p. 808-816.	2016-2018	[30]
Dybdahl, D., et al., Four-factor prothrombin complex concentrate for the reversal of factor Xa inhibitors for traumatic intracranial hemorrhage. Am J Emerg Med, 2019. 37(10): p. 1907-1911.	2015-2017	[20]
Frontera, J.A., et al., Cost comparison of andexanet versus prothrombin complex concentrates for direct factor Xa inhibitor reversal after hemorrhage. J Thromb Thrombolysis, 2020. 49(1): p. 121-131.	2014-2018	[7]
Berger, K., et al., A Low-Dose 4F-PCC Protocol for DOAC-Associated Intracranial Hemorrhage. J Intensive Care Med, 2019: p. 885066619840992.	2014-2015	[19]
Grandhi, R., et al., Administration of 4-Factor Prothrombin Complex Concentrate as an Antidote for Intracranial Bleeding in Patients Taking Direct Factor Xa Inhibitors. World Neurosurg, 2015. 84(6): p. 1956-61.	2013-2015	[22]
Harrison, S.K., et al., Comparison of outcomes in patients with intracranial hemorrhage on factor Xa inhibitors versus vitamin K antagonists treated with 4-factor prothrombin complex concentrate. Proc (Bayl Univ Med Cent), 2018. 31(2): p. 153-156.	2013-2015	[23]
Majeed, A., et al., Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. Blood, 2017. 130(15): p. 1706-1712.	2014-2016	[26]
Muller, M., et al., Application of prothrombin complex concentrate for reversal of direct oral anticoagulants in clinical practice: indications, patient characteristics and clinical outcomes compared to reversal of vitamin K antagonists. Scand J Trauma Resusc Emerg Med, 2019. 27(1): p. 48.	2012-2017	[24]
Santibanez, M., et al., Tolerability and effectiveness of 4-factor prothrombin complex concentrate (4F-PCC) for warfarin and non-warfarin reversals. J Crit Care, 2018. 48: p. 183-190.	2014-2015	[38]
Schenk, B., et al., Four-factor prothrombin complex concentrate improves thrombin generation and prothrombin time in patients with bleeding	2014-2016	[31]

Publikation	Studieperiode	Ref
complications related to rivaroxaban: a single-center pilot trial. Thromb J, 2018. 16: p. 1.		
Schulman, S., et al., Prothrombin Complex Concentrate for Major Bleeding on Factor Xa Inhibitors: A Prospective Cohort Study. Thromb Haemost, 2018. 118(5): p. 842-851.	2014-2017	[28]
Sheikh-Taha, M., Treatment of apixaban- and rivaroxaban-associated major bleeding using 4-factor prothrombin complex concentrate. Intern Emerg Med, 2019. 14(2): p. 265-269.	2016-2018	[13]
Sin, J.H., K. Berger, and C.A. Lesch, Four-factor prothrombin complex concentrate for life-threatening bleeds or emergent surgery: A retrospective evaluation. J Crit Care, 2016. 36: p. 166-172.	2014	[37]
Smith, M.N., et al., Safety, efficacy, and cost of four-factor prothrombin complex concentrate (4F-PCC) in patients with factor Xa inhibitor-related bleeding: a retrospective study. J Thromb Thrombolysis, 2019. 48(2): p. 250-255.	2014-2018	[15]
Allison, T.A., et al., Evaluation of the Use of Low-Dose 4-Factor Prothrombin Complex Concentrate in the Reversal of Direct Oral Anticoagulants in Bleeding Patients. J Intensive Care Med, 2018: p. 885066618800657.	2013-2015	[12]
Tao, J., E.N. Bukanova, and S. Akhtar, Safety of 4-factor prothrombin complex concentrate (4F-PCC) for emergent reversal of factor Xa inhibitors. J Intensive Care, 2018. 6: p. 34.	2013-2017	[16]
Tellor, K.B., N.S. Barasch, and B.M. Lee, Clinical experience reversing factor Xa inhibitors with four-factor prothrombin complex concentrate in a community hospital. Blood Transfus, 2018. 16(4): p. 382-386.	2014-2016	[32]
Testa, S., et al., Management of major bleeding and outcomes in patients treated with direct oral anticoagulants: results from the START-Event registry. Intern Emerg Med, 2018. 13(7): p. 1051-1058.	2015	[29]

Bilag 2:Matching-kriterier (*propensity score matching*) for sammenligning af data fra ORANGE og ANNEXA-4



Bilag 3: Effektestimater for dødelighed i PKK-studier

Studie	PKK behandling	N	Effektestimater	Tidsramme
Allison et al. (2018)	PKK 35 U/kg	31	15 %	Ukendt
Arachchillage et al. (2019)	PKK 16,7-50 U/kg (rivaroxaban; middel 26,8) og 18,5-43 U/kg (apixaban; middel 25)	80 (40 apixaban, 40 rivaroxaban)	Samlet: 33 % Apixaban: 33,5 % Rivaroxaban: 32,5 % ICH: Apixaban: 38,1 % Rivaroxaban: 44 %	30-dages dødelighed
Berger et al. (2019)	PKK 25 U/kg	22	18,2 %	Dødelighed under indlæggelse
Dybdahl et al. (2019)	PKK anbefalet dosis var 50 U/kg	62	22,9 % Epidural haematoma: 0 % Subdural haematoma: 27 % Subarachnoid haemorrhage: 29 % Intracerebral haemorrhage: 50 %	Dødelighed under indlæggelse
Gerner et al. (2018)	PKK mediandosis 2000 IU	103 patienter fik PKK; inkl. 9 patienter behandlet med dabigatran	19,4 % (20/103)	Dødelighed under indlæggelse 29,1 % (30/103)
Grandhi et al. (2015)	PKK median dosis 3177 IU (2124-4770)	18	33 %	Dødelighed under indlæggelse
Harrison et al. (2018)	PKK anbefalet dosis var 50 U/kg	14 behandlet med DOACs	14,2 %	Dødelighed under indlæggelse
Majeed et al. (2017)	PKK mediandosis 2000 IU (1500-2000) Apixaban 26,7 U/kg (22,0-29,9) Rivaroxaban 26,7 U/kg (20,8-29,4)	84	Samlet: 32 % ICH: 33,9 %	30-dages dødelighed
Muller et al. (2019)	PKK mediandosis 2000 IU (1700-3000) blandt alle DOAK patienter (inkl. non-bleed)	69 DOAK-relatede major bleedings	9,5 %	Dødelighed under indlæggelse
Schenk et al. (2018)	PKK 25 U/kg	13	23,1 %	30-dages dødelighed
Schulman et al. (2018)	PKK 2000 IU	66	Samlet: 14 % ICH: 22,2 % (8/36)	Dødelighed under indlæggelse
Sheikh-Taha (2019)	PKK 50 U/kg	29	Samlet: 20,7 % Rivaroxaban: 12,5 % Apixaban: 30,8 % All deaths were ICH, dvs 28,6 % of ICH patienter døde	Dødelighed under indlæggelse
Smith et al. (2019)	PKK 38,7 % fik 25 U/kg; 51,6 % fik 50 U/kg	31	16,1 %	Dødelighed under indlæggelse

Studie	PKK behandling	N	Effektestimater	Tidsramme
Tao et al. (2018)	PKK mest 25-50 U/kg	43	2,3 % (1/43)	Ukendt
Tellor et al. (2018)	PKK 50 U/kg, 25 U/kg or 10 U/kg; anbefalet var 50	27 DOAC-related MBs	Overall: 14,8 % (4/27) ICH: 50 % (3/6) Intraperitoneal: 100 % (1/1)	Dødelighed under indlæggelse
Testa et al. (2018)	PKK – dosis ukendt	5 behandlet med apixaban og 15 behandlet med rivaroxaban behandlet med PKK	Overall: 20 % (4/20) Apixaban: 20 % (1/5) Rivaroxaban: 20 % (3/15)	Dødelighed indenfor 1-3 dage

Medicinrådet

Application for the assessment of andexanet alfa (Ondexxya®) for adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding

Contents

List of Tables

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1 Basic information

TABLE 1. CONTACT INFORMATION

Name	Martijn Negen
Title	General Manager Netherlands & Nordics
Area of responsibility	Commercial
Phone	+31 (0)6 46 82 7979
E-mail	mnegen@portola.com

TABLE 2. OVERVIEW OF THE PHARMACEUTICAL

Proprietary name	Ondexxya®
Generic name	Andexanet alfa
Marketing authorization holder in Denmark	Portola Netherlands B.V.
ATC code	V03AB38
Pharmacotherapeutic group	All other therapeutic products, antidotes
Active substance(s)	Andexanet alfa
Pharmaceutical form(s)	Powder for solution for infusion
Mechanism of action	Andexanet alfa is a recombinant form of human FXa protein that has been modified to lack FXa enzymatic activity. The active site serine was substituted with alanine, rendering the molecule unable to cleave and activate prothrombin, and the gamma-carboxyglutamic acid (Gla) domain was removed to eliminate the ability of the protein to assemble into the prothrombinase complex, thus removing any anti-coagulant effects. Andexanet alfa is a specific reversal agent for FXa inhibitors. The predominant mechanism of action is the binding and sequestration of the FXa inhibitor, although there may be a minor contribution from the inhibition of tissue factor pathway inhibitor (TFPI) activity through binding to TFPI. The interaction between andexanet alfa and TFPI has not been fully characterised. Andexanet alfa binds direct FXa inhibitors with high affinity, making them unavailable to exert their anticoagulant effects.
Dosage regimen	Andexanet alfa is a one-time treatment administered as an intravenous bolus at a target rate of approximately 30 mg/min over 15 minutes (low dose) or 30 minutes (high dose), followed by administration of a continuous infusion of 4 mg/min (low dose) or 8 mg/min (high dose) for 120 minutes. Dosing regimens: Low dose 400 mg at a target rate of 30 mg/min and 4 mg/min for 120 minutes (480 mg), 5 vials High dose 800 mg at a target rate of 30 mg/min and 8 mg/min for 120 minutes (960 mg), 9 vials

Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	For adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
Other approved therapeutic indications	None
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	None
Packaging – types, sizes/number of units, and concentrations	Powder for solution for infusion, 4 vials, 200 mg
Orphan drug designation	Andexanet alfa has Orphan Drug Designation in USA. However, the reason why EMA did not designate it Orphan Drug in EU is that the major bleed is a condition, not a disease.

2 Abbreviations

AF	Atrial fibrillation
aPCC	Activated prothrombin complex concentrates
aPTT	Activated partial thromboplastin time
ASD	Absolute standardized difference
CI	Confidence Interval
CT	Computed tomography
dFXaI	Direct factor Xa inhibitor
DOAC	Direct oral anticoagulant
DSU	The decision support unit
DVT	Deep vein thrombosis
EMA	European Medicines Agency
ETP	Endogenous thrombin potential
FXa	Factor Xa
GCS	Glasgow coma scale
GI	Gastrointestinal
ICH	Intracranial haemorrhage
ICU	Intensive care unit
INR	International normalised ratio
IQR	Interquartile range
ISTH	International Society on Thrombosis and Haemostasis
ISTH/SSC	The Scientific and Standardization Committee of ISTH
IU	International units
LOS	Length of stay
MB	Major bleed
MD	Mean difference
MI	Myocardial infarction
MRI	Magnetic resonance imaging
mRS	modified Rankin scale
NICE	National Institute for Heath and Care Excellence

NVAF	Non-valvular atrial fibrillation
PCC	Prothrombin complex concentrates
PE	Pulmonary embolism
PT	Prothrombin time
RR	Relative risk
SoC	Standard of care
SPAF	Stroke prevention atrial fibrillation
SSC/ISTH	The Scientific and Standardization Committee of ISTH
TBI	Traumatic brain injury
TE	Thromboembolic event
TFPI	Tissue factor pathway inhibitor
TIA	Transient ischaemic attack
VT/VTE	Venous thromboembolism

3 Summary

This application to the Danish Medicine Council considers the use of andexanet alfa in Danish medical practice for the treatment of life-threatening or uncontrolled bleeds related to the two direct factor Xa inhibitors apixaban and rivaroxaban.

Andexanet alfa is a recombinant modified version of human FXa protein that, other than any currently used reversal agent, rapidly binds and sequesters FXa inhibitors and reduces the concentration of the unbound inhibitors, thereby neutralizing their anticoagulant effects. This allows for the restoration of haemostasis via endogenous native FXa. Andexanet alfa is a specific reversal agent for the management of major FXa inhibitor-related bleeding and clinical trials indicate that andexanet alfa may fulfil the significant unmet medical need.

Danish guidelines published in 2016 [1], prior to the EMA approval of andexanet alfa, recommend the use of prothrombin complex concentrates (PCCs) to prevent the anticoagulant effects of FXa inhibitors. However, it is important to note that PCCs are not EMA-approved for administration in patients with FXa inhibitor-associated bleeding. In addition, andexanet alfa has been recommended in numerous guidelines from a range of international specialist organisations involved in managing life threatening and uncontrolled bleeds, these are described further in Appendix 7.3. [6-16] As a part of this application, a literature review was made to identify substantial clinical evidence in bleeding patients to support the safety and effectiveness of andexanet alfa in comparison to current therapies used off-label, such as PCCs. The literature search was conducted using search strings provided by DMC and included 181 articles included for screening, whereof 25 were included in the qualitative synthesi. Four articles were studies of andexanet alfa and 19 were studies of PCC, the last two were unpublished indirect comparisons between the two, added by the applicant.

Outcomes of interest were 30-day mortality (reported in 22 articles), change in mRS scores (reported in 3 articles), proportion of patients achieving effective hemostasis (reported in 21 articles) and the proportion of patients experiencing thromboembolic events (reported in 23). A qualitative review of adverse and thromboembolic events was also conducted where applicable. Studies reporting change in EQ-5D scores were missing. Generally, the outcomes were measured within different time frames and using different methods and definitions, making it difficult to draw conclusions only from considering the results of different studies. However, the recent studies from the UK and Germany used in the indirect comparison suggest that andexanet alfa is a more effective option in reducing 30 day mortality. The ORANGE (Oral anticoagulant agent-associated bleeding events reporting system) study conducted in the UK showed that

the use of 4F-PCC was not predictive of the cumulative risk of death. The ORANGE [2] data was later used in combination with the ANNEXA-4 [3] data to compare the effect of PCCs and andexanet alfa on 30-day mortality through a propensity score matching analysis (PSM), showing, most notably that ICH and GI patients receiving andexanet alfa rather than PCC had a more than 3-fold and 2-fold improvement in survival after 30 days, respectively.[4] Combining data from the ANNEXA-4 study [3] with the German-Wide Multicenter Analysis of Oral Anticoagulation–Associated Intracerebral Hemorrhage; part II (RETRACE II) study [5, 6] in a similar way showed that andexanet alfa was more effective in reaching hemostasis than the standard of care (SoC; a statistically significant 7.12 ml higher mean change from baseline ICH volume) in patients with ICH. The analysis also showed that estimates for difference in means of post-treatment mRS had a numerical advantage, although statistically insignificant, of andexanet alfa over SoC.[4]

Andexanet alfa is a specific reversal agent that is generally well-tolerated and rapidly reverses anticoagulation in patients treated with rivaroxaban or apixaban who have life-threatening or uncontrolled bleeding. Findings from the andexanet alfa clinical development program provide compelling support for a well-tolerated novel therapeutic agent for the reversal of anticoagulation and will offer patients and clinicians a specific reversal strategy for managing FXa inhibitor-associated bleeding. Given the wide adoption of FXa inhibitors in Denmark, andexanet alfa may present an effective option to current SoC for the urgent reversal of FXa inhibitor-associated uncontrolled and life-threatening bleeds where therapeutic options are limited, and an unmet medical need exists.

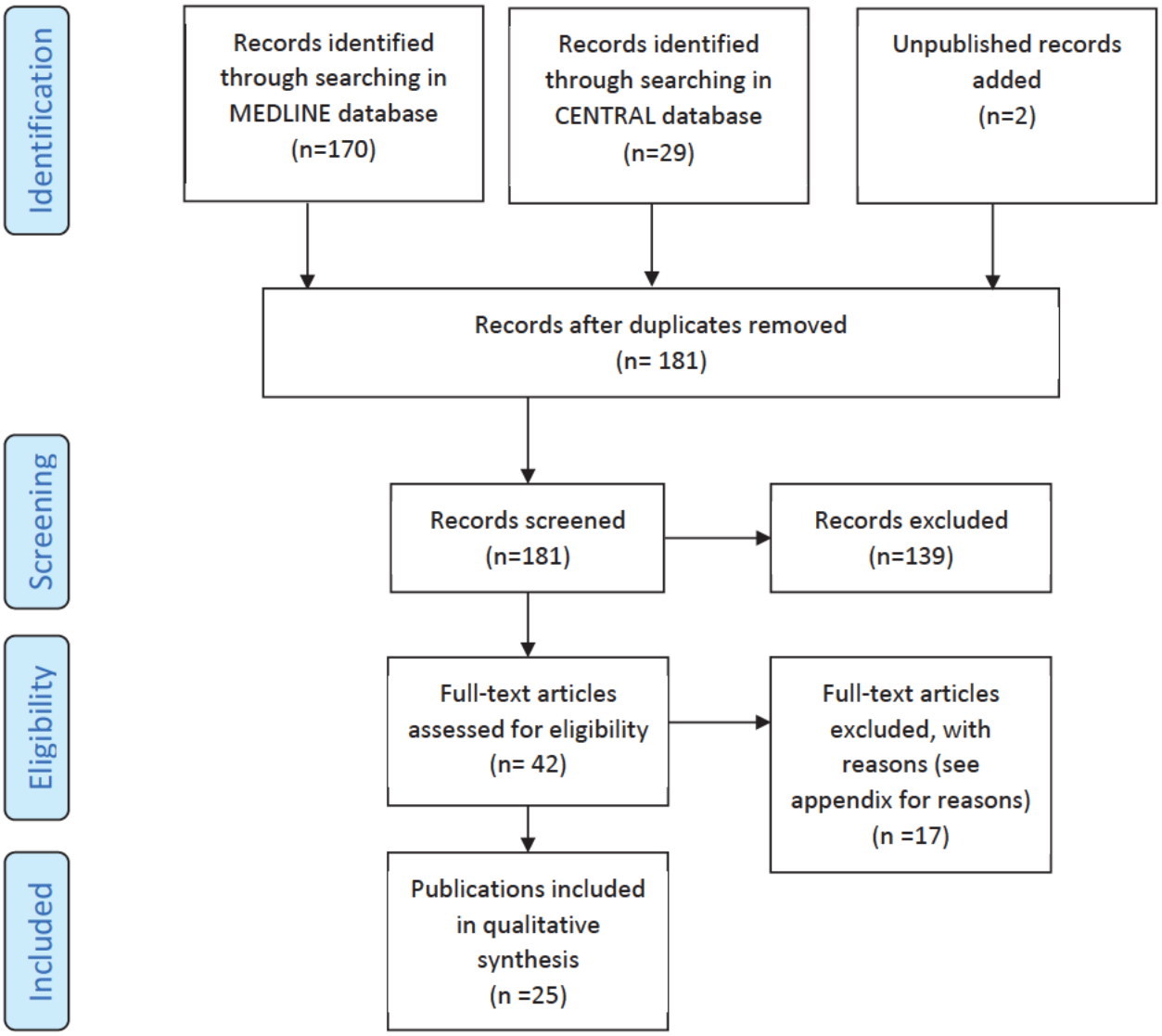
4 Literature search

Figure 1 displays the process for reviewing records for inclusion. As specified in the protocol, the literature search was carried out in the MEDLINE and CENTRAL databases, accessed via PubMed and Cochrane Library, respectively. The search in PubMed and Cochrane Library was carried out on January 17, 2020 and gave 170 and 29 hits, respectively in each database. Only studies on patients with major bleeds were included. Prothrombin complex concentrates (PCC) are regarded as standard of care in Denmark, and to our knowledge no guidelines mention aPCC. Hence studies on aPCC were excluded. See Appendix 7.1 for inclusion and exclusion criteria.

In addition, two unpublished analyses were added in agreement with the secretary of the Danish Medicine Council; ANNEXA-4 compared to ORANGE, and ANNEXA-4 compared to RETRACE II. These studies were added as they are currently the only studies comparing andexanet alfa to PCC – as there is no head to head comparison between the medicines, the analyses were conducted by matching the original datasets of ORANGE and RETRACE II with ANNEXA-4 using propensity score matching (PSM). The ORANGE database is a well-established database in the UK from which multiple publications have emerged and the data has been accepted by NICE in the UK as part of the review process. The ORANGE data was presented as a poster on the American College of Cardiology Congress in March 2020. Similarly, the RETRACE II database is a well-established German database which has also led to several publications within the area of bleeding management and has been accepted by the German AMNOG as part of the review process. The RETRACE II data will be presented orally and as a poster at the European Stroke Organisation Congress in November 2020. Furthermore, both datasets will be submitted for publication in peer-reviewed journals.

After the removal of duplicates, 181 records were screened by title and abstract. 42 records were reviewed in full, leaving 25 articles for the systematic review. Reasons for exclusion are provided in Appendix 7.1.

FIGURE 1. PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META-ANALYSES (PRISMA) FLOW CHART OF STUDY SELECTION



4.1 Relevant studies

A total of 25 publications were included in the qualitative synthesis, 23 relevant publications were identified from the literature search and two unpublished analyses were added. Table 3 below lists each publication included in the assessment and its relevance for the clinical question and the different outcomes.

TABLE 3. RELEVANT PUBLICATIONS INCLUDED IN THE ASSESSMENT

Reference	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for outcome[§]
Allison, T.A., et al., Evaluation of the Use of Low-Dose 4-Factor Prothrombin Complex Concentrate in the Reversal of Direct Oral Anticoagulants in			1 May 2013-15 June 2015	1,3,4,5

Bleeding Patients. J Intensive Care Med, 2018: p. 885066618800657. [7]				
Arachchillage, D.R.J., et al., Efficacy and safety of prothrombin complex concentrate in patients treated with rivaroxaban or apixaban compared to warfarin presenting with major bleeding. Br J Haematol, 2019. 184(5): p. 808-816. [8]			January 2016-April 2018	1,3,4,5
Berger, K., et al., A Low-Dose 4F-PCC Protocol for DOAC-Associated Intracranial Hemorrhage. J Intensive Care Med, 2019: p. 885066619840992. [9]			March 2014-December 2015	1,3,4,5
Brown, C.S., et al., Real-world utilization of andexanet alfa. Am J Emerg Med, 2019. [10]			July 2018-April 2019	1,3,4
Connolly, S.J., et al., Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. N Engl J Med, 2016. 375(12): p. 1131-41.[11]	ANNEXA-4	NCT02329327	April 2015-	1,2,3,4,5
Connolly, S.J., et al., Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med, 2019. 380(14): p. 1326-1335.[12]	ANNEXA-4	NCT02329327	April 2015-May 2018	1,3,4,5
Dybdahl, D., et al., Four-factor prothrombin complex concentrate for the reversal of factor Xa inhibitors for traumatic intracranial hemorrhage. Am J Emerg Med, 2019. 37(10): p. 1907-1911.[13]			1 March 2015-31 August 2017	1,4,5
Frontera, J.A., et al., Cost comparison of andexanet versus prothrombin complex concentrates for direct factor Xa inhibitor reversal after hemorrhage. J Thromb Thrombolysis, 2020. 49(1): p. 121-131.[14]			1 January 2014-15 July 2018	3,4,5
Gerner, S.T., et al., Association of prothrombin complex concentrate administration and hematoma enlargement in non-vitamin K antagonist oral anticoagulant-related intracerebral hemorrhage. Ann Neurol, 2018. 83(1): p. 186-196.[5]	RETRACE II	NCT03093233	2011-2015	1,3
Grandhi, R., et al., Administration of 4-Factor Prothrombin Complex Concentrate as an Antidote for Intracranial Bleeding in Patients Taking Direct Factor Xa Inhibitors. World Neurosurg, 2015. 84(6): p. 1956-61.[15]			August 2013-February 2015	1,3,5
Harrison, S.K., et al., Comparison of outcomes in patients with intracranial hemorrhage on factor Xa inhibitors versus vitamin K antagonists treated with 4-factor prothrombin complex concentrate. Proc (Bayl Univ Med Cent), 2018. 31(2): p. 153-156.[16]			July 2013-December 2015	1,3,4,5
Majeed, A., et al., Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. Blood, 2017. 130(15): p. 1706-1712.[17]			1 January 2014-1 October 2016	1,3,4,5
Muller, M., et al., Application of prothrombin complex concentrate for reversal of direct oral anticoagulants in clinical practice: indications, patient characteristics and clinical outcomes compared to reversal of vitamin K antagonists. Scand J Trauma Resusc Emerg Med, 2019. 27(1): p. 48.[18]			1 June 2012-1 July 2017	1
Santibanez, M., et al., Tolerability and effectiveness of 4-factor prothrombin complex concentrate (4F-PCC) for warfarin and non-warfarin reversals. J Crit Care, 2018. 48: p. 183-190.[19]			March 2014-December 2015	3,4
Schenk, B., et al., Four-factor prothrombin complex concentrate improves thrombin generation and prothrombin time in patients with bleeding complications related to rivaroxaban: a single-center pilot trial. Thromb J, 2018. 16: p. 1.[20]			August 2014-October 2016	1,3,4,5
Schulman, S., et al., Prothrombin Complex Concentrate for Major Bleeding on Factor Xa Inhibitors: A Prospective Cohort Study. Thromb Haemost, 2018. 118(5): p. 842-851.[21]			July 2014-July 2017	1,3,4,5
Sheikh-Taha, M., Treatment of apixaban- and rivaroxaban-associated major bleeding using 4-factor			1 June 2016-30 June 2018	1,3,4,5

prothrombin complex concentrate. Intern Emerg Med, 2019. 14(2): p. 265-269.[22]				
Sin, J.H., K. Berger, and C.A. Lesch, Four-factor prothrombin complex concentrate for life-threatening bleeds or emergent surgery: A retrospective evaluation. J Crit Care, 2016. 36: p. 166-172.[23]			1 March 2014-31 December 2014	3,4,5
Smith, M.N., et al., Safety, efficacy, and cost of four-factor prothrombin complex concentrate (4F-PCC) in patients with factor Xa inhibitor-related bleeding: a retrospective study. J Thromb Thrombolysis, 2019. 48(2): p. 250-255.[24]			1 July 2014-30 May 2018	1,3,4
Stevens, V.M., et al., Coagulation Factor Xa (Recombinant), Inactivated-Zhzo (Andexanet Alfa) Hemostatic Outcomes and Thrombotic Event Incidence at an Academic Medical Center. Clin Appl Thromb Hemost, 2019. 25: p. 1076029619896619.[25]			June 2018-August 2019	1,3,4,5
Tao, J., E.N. Bukanova, and S. Akhtar, Safety of 4-factor prothrombin complex concentrate (4F-PCC) for emergent reversal of factor Xa inhibitors. J Intensive Care, 2018. 6: p. 34.[26]			January 2013-May 2017	1,3,4,5
Tellor, K.B., N.S. Barasch, and B.M. Lee, Clinical experience reversing factor Xa inhibitors with four-factor prothrombin complex concentrate in a community hospital. Blood Transfus, 2018. 16(4): p. 382-386.[27]			2014-2016	1,4,5
Testa, S., et al., Management of major bleeding and outcomes in patients treated with direct oral anticoagulants: results from the START-Event registry. Intern Emerg Med, 2018. 13(7): p. 1051-1058.[28]			1 January 2015-31 December 2016	1,4
ANNEXA-4 compared to ORANGE				1
ANNEXA-4 compared to RETRACE II				1,2,3
§ Outcomes: 1: Proportion of patients dying within 30 days, 2: Difference in change measured on MRS from baseline to after 30 days, 3: Proportion of patients who achieve effective haemostasis within 48 hours 4: Qualitative review of adverse reaction profile and safety aspects and 5: Difference in change in EQ-5D index score				

4.2 Main characteristics of included studies

The main characteristics from the included studies are summarised in Appendix 7.2. Only one relevant clinical trial (ANNEXA-4) was identified. The ANNEXA-4 study is presented below.

ANNEXA-4

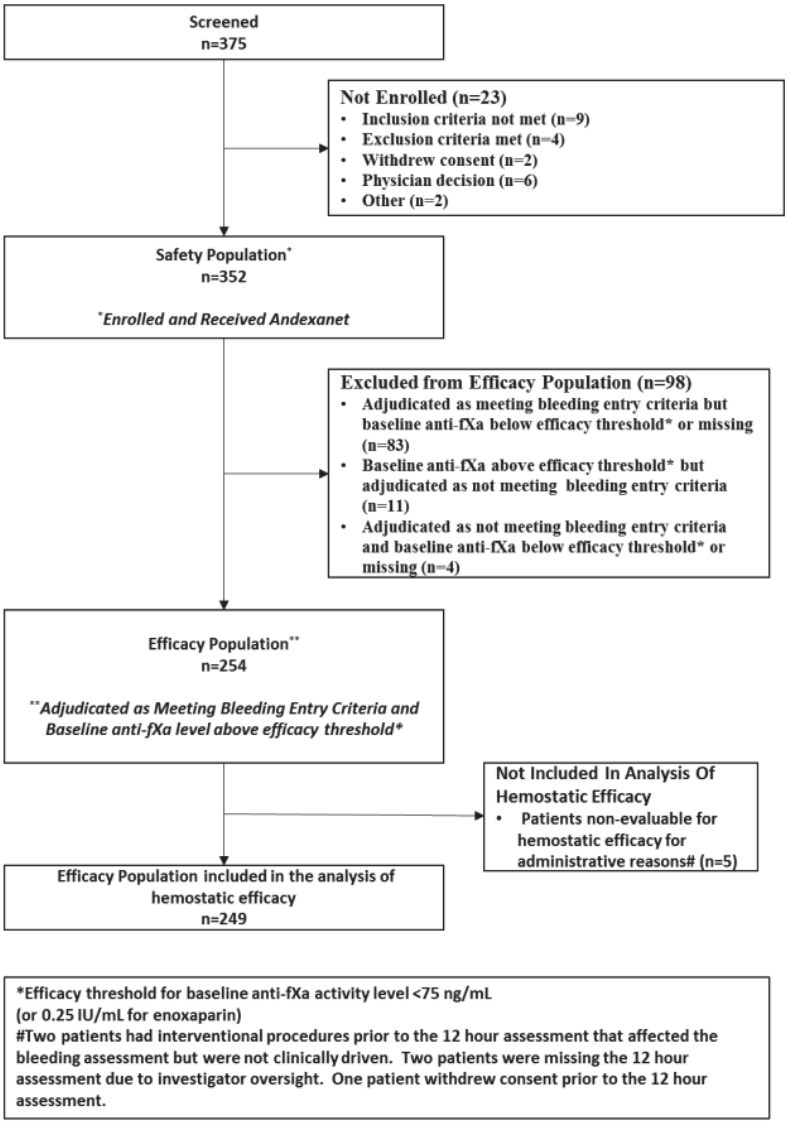
ANNEXA-4 was a phase 3b/4, prospective, open-label, single-arm study designed to evaluate the efficacy and safety of andexanet alfa in patients receiving a FXa inhibitor (apixaban, rivaroxaban, edoxaban, or enoxaparin) who presented with acute major bleeding.[29] After the complete enrolment of the primary cohort, an extension of the ANNEXA-4 study continues to enrol patients in Germany to gain experience of edoxaban patients. There is also an extension arm enrolling in Japan with the purpose of gaining experience in an Asian population.

Patients received andexanet alfa administered as IV bolus, immediately followed by a 2-hour continuous infusion. Two dosing regimens (low dose or high dose) were used based on the type and dose of FXa inhibitor and timing of the last dose received. The primary endpoints were the percent change from baseline in anti-FXa activity and the occurrence of “effective haemostasis” as judged by an independent endpoint adjudication committee. CT-scans were performed for all ICH-patients at given timepoints to assess haematoma expansion.

Patients enrolled in ANNEXA-4 represented a very high-risk population. All 352 patients received a bolus and subsequent andexanet alfa infusion and were followed for 30 days or until death.

The efficacy analysis population included 254 patients who retrospectively met both of two criteria: baseline anti-FXa activity ≥75 ng/mL (or ≥0.25 IU/mL for enoxaparin); and confirmed major bleeding at presentation. Of the 254 patients in the efficacy analysis, 249 could be evaluated for haemostatic efficacy which included subjects determined by external adjudication committee whom had 1) met definition of major bleeding as per protocol, 2) had baseline anti-Xa activity ≥75 ng/mL and 3) had efficacy measurements at baseline and 12 hours available and did not have any relevant major protocol deviation affecting primary haemostatic efficacy assessment.

FIGURE 2. CONSORT DIAGRAM



5 Clinical questions

The clinical question was specified in the protocol as *"Hvad er værdien af andexanet alfa sammenlignet med protrombinkomplexkoncentrat til patienter, som modtager direkte faktor Xa-hæmmer og har livstruende eller ukontrolleret blødning?"* meaning *"What is the added value of andexanet alfa compared to prothrombin complex concentrates in treating patients administered direct factor Xa inhibitors experiencing life-threatening or uncontrolled bleeding?"*

5.1 Presentation of relevant studies

Ondexxya▼® (andexanet alfa) is the only treatment approved by the EMA for patients treated with the FXa inhibitors rivaroxaban or apixaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. The effect of andexanet alfa on DOAC reversal has been studied in an extensive clinical program including numerous of studies from phase I to phase IIIb. The ANNEXA-4 trial has studied the effect of andexanet alfa on patients with uncontrolled or major bleeding. Based on the search protocol provided by the DMC four studies relating to andexanet alfa were found, two of them constituted the ANNEXA-4 trial [11, 12] and two were retrospective studies [10, 25].

It is important to note that there are numerous reasons not to consider PCCs the standard of care for the indication of andexanet alfa, among other things, PCCs do not affect plasma anti-FXa activity nor normalise thrombin generation in the presence of therapeutic anti-FXa levels.[30, 31] Furthermore, there is no mechanistic rationale for reversal of anti-FXa activity by PCC as patients on FXa inhibitors are not factor depleted and PCCs have not demonstrated any impact on therapeutic anti-FXa levels.[32] Neither are PCCs EMA-approved for administration in patients with FXa inhibitor-associated bleeding and there is no substantial clinical trial evidence in bleeding patients to support the safety and effectiveness of off-label use of PCCs, resulting in a wide variety of doses recommended and used in the studies presented below. The effect of PCCs on DOAC reversal in patients with life-threatening or uncontrolled bleeding has been studied in 15 retrospective studies [5, 7-9, 13-16, 18, 19, 22-24, 26, 27] and four prospective studies [17, 20, 21, 28]. Lastly, although PCCs in the recent past have been used in an attempt to reverse DOACs, numerous international guidelines from various specialist organisations have in the past few years been revised to prefer andexanet or a specific reversal agent over PCCs.[33-43] These guidelines are further described in Appendix 7.3.

Two studies indirectly comparing andexanet alfa to PCC were included independent of the search protocol. The first of the two used 30-day mortality as an outcome to compare the effect of andexanet alfa compared to PCC using data from the UK population in ORANGE and ANNEXA-4 studies.[2, 12] The second used data collected during the German RETRACE II study and ANNEXA-4 data to compare how andexanet alfa did in comparison with PCC in 30-day mortality, change in mRS scores and effectiveness in reaching haemostasis among patients experiencing intracranial haemorrhages (ICH).[5, 6, 12]

5.2 Results per outcome

In the following section the results per outcome, as specified in the protocol, are presented. No indirect comparison was done due to large heterogeneity between the published studies. There are significant differences in inclusion and exclusion criteria, not only between andexanet alfa and PCC studies but importantly also between the PCC studies themselves. PCC studies not only differ in the PCC dose used but the amount of FXa may differ between and within PCC brands, rendering it difficult if not impossible to determine how much FXa, which is the component of 4F-PCC considered important in this context, is administered to a patient. These issues have also been highlighted in a study investigating studies of PCC by Costa et al.[44], which to a great extent overlaps the studies included in this application. Costa et al.[44] in

their review of methodological and reporting quality in case series of 4F-PCCs conclude that "although many case series describing off-label use of 4F-PCC for reversing FXa-related bleeding have been published, the presence of methodological flaws and/or poor reporting necessitates caution in interpretation." Examples of such flaws noted in the studies presented in this application include no measurements of DOAC activities in PCC studies (this was included in andexanet alfa studies) and baseline CT scans not being conducted in most PCC studies, contrary to andexanet alfa studies. Post-treatment CT scans were taken at different time intervals and in some PCC cases not at all (physician interpretation, often subjective, was used to determine thrombostatic efficacy).

Table 4 shows the number of studies per outcome and treatment. The data avalability was limited for some of the requested outcomes.

TABLE 4. NUMBER OF STUDIES PER OUTCOME AND TREATMENT

	Andexanet alfa	PCC	Andexanet alfa + PCC
Total number of studies	4	19	2
Number of studies reporting mortality, whereof	4	16	2
- 30-day mortality	4	3	2
- 1-3 day mortality	-	1	-
- In-hospital mortality	-	10	-
- No specified time frame	-	2	-
Number of studies reporting mRS	1	0	1
Number of studies reporting efficacy, whereof	4	14	1
- Within 48 hours	-	1	-
- Within 24 hours	-	5	-
- Within 12 hours	4	-	1*
- No specified timeframe	-	8	-
Number of studies reporting thromboembolic events, whereof	4	17	0
- Within 30 days	4	6	-
- Within 15 days	-	1	-
- Within 14 days	-	4	-
- In-hospital thromboembolic events	-	6	-
Number of studies reporting EQ-5D	0	0	0

*Follow-up for patients administered andexanet alfa was within 12 hours; follow-up for PCC was for the majority of patients within 36 hours.

5.2.1 Proportion of patients dying within 30 days

The protocol states that the rate of patients dying within 30 days is the most relevant mortality outcome. The results presented below in Table 5 presents the proportion of patients dying within 30 days, and mortality outcomes with other follow-up periods. All andexanet alfa studies (4) report 30-day mortality. PCC studies report 30-day mortality (3), death within 1-3 days (1), in-hospital mortality (10) and no timeframe (2). The comparison for 30-day mortality is biased into disadvantage compared to a shorter period, as deaths occurring between the specified timeframe and day 30 are not captured.

In the ANNEXA-4 safety-population, the overall mortality was 14%.[12]

The three analyses reporting overall 30-day mortality following treatment with PCC for reversal of FXa inhibitors shows varying estimates from 23.1% to 33% [8, 17, 20]; as expected, estimates of in-hospital mortality are generally relatively lower, ranging from 9.5% to 33% [5, 9, 13, 15, 16, 18, 21, 22, 24, 27]. The remaining three studies included reported deaths within 1-3 days and deaths within an unknown

timeframe – however, these studies likely also to refer to in-hospital mortality with a rate of mortality ranging from 2.3% to 20% [7, 26, 28].

TABLE 5. RESULTS REFERRING TO PROPORTION OF PATIENTS DYING WITHIN 30 DAYS

Results per treatment	Studies included in the analysis	Treatment	N	Estimate	Methods used for quantitative synthesis
Andexanet alfa	Brown et al. (2019)[10]	Andexanet alfa (27% [6/22] on high dose, 73% on low)	22	Overall: 24% ICH: 23% (3/13) GI: 25% (1/4)	Based on Connolly et al. (2016)
	Connolly et al. (2016)[11]	Andexanet alfa	67	Overall: 15% ICH: 21,4% (6/28) GI: 6% (2/33) Other: 33% (2/6)	30-day mortality. The prespecified safety population included all the patients who received andexanet.
	Connolly et al. (2019)[12]	Andexanet alfa	352	14%	Based on Connolly et al. (2016)
	Stevens et al. (2019)[25]	Andexanet alfa (15% on high dose, 85% on low)	13	Overall: 15% ICH: 33% (2/6)	Based on Connolly et al. (2016)
PCC	Allison et al. (2018) [7]	PCC 35 U/kg	31	15%	Timeframe unknown
	Arachchillage et al. (2019) [8]	PCC 16,7-50 U/kg (rivaroxaban; mean 26,8) and 18,5-43 U/kg (apixaban; mean 25)	80 (40 on apixaban, 40 on rivaroxaban)	Overall: 33% Apixaban: 33,5% Rivaroxaban: 32,5% ICH: Apixaban: 38,1% Rivaroxaban: 44%	30-day mortality.
	Berger et al. (2019) [9]	PCC 25 U/kg	22	18,2%	In-hospital mortality
	Dybdahl et al. (2019) [13]	PCC recommended dose was 50 U/kg	62	22,9% Epidural haematoma: 0% Subdural haematoma: 27% Subarachnoid haemorrhage: 29% Intracerebral haemorrhage: 50%	In-hospital mortality
	Gerner et al. (2018) [5]	PCC median dose 2000 IU	103 patients received PCC; includes 9 patients on dabigatran	19,4% (20/103)	In-hospital mortality. 29,1% (30/103) dead within 3 months – corresponding estimates for patients with no PCC prior to follow-up was 20,9% and 30,2%
	Grandhi et al. (2015) [15]	PCC median dose 3177 IU (2124-4770)	18	33%	In-hospital mortality
	Harrison et al. (2018) [16]	PCC recommended dose was 50 U/kg	14 on DOACs	14,2%	In-hospital mortality
	Majeed et al. (2017) [17]	PCC median dose 2000 IU (1500-2000) Apixaban 26.7 U/kg (22.0-29.9) Rivaroxaban 26.7 U/kg (20.8-29.4)	84	Overall: 32% ICH: 33,9%	30-day mortality
	Muller et al. (2019) [18]	PCC median dose 2000 IU (1700-3000) among all DOAC patients (including non-bleed)	69 DOAC-related MBs	9,5%	In-hospital mortality
	Schenk et al. (2018) [20]	PCC 25 U/kg	13	23,1%	30-day mortality
	Schulman et al. (2018) [21]	PCC 2000 IU	66	Overall: 14% ICH: 22,2% (8/36)	In-hospital mortality
	Sheikh-Taha (2019) [22]	PCC 50 U/kg	29	Overall: 20,7% Rivaroxaban: 12,5% Apixaban: 30,8% All deaths were ICH, meaning 28,6% of ICH patients died	In-hospital mortality
	Smith et al. (2019) [24]	PCC 38,7% received 25 U/kg; 51,6% received 50 U/kg	31	16,1%	In-hospital mortality
	Tao et al. (2018) [26]	PCC mainly 25-50 U/kg	43	2,3% (1/43)	Timeframe unknown
	Tellor et al. (2018) [27]	PCC 50 U/kg, 25 U/kg or 10 U/kg; recommended was 50	27 DOAC-related MBs	Overall: 14,8% (4/27) ICH: 50% (3/6) Intraperitoneal: 100% (1/1)	In-hospital mortality

	Testa et al. (2018)[28]	PCC – dose unknown	5 on apixaban and 15 on rivaroxaban treated with PCC	Overall: 20% (4/20) Apixaban: 20% (1/5) Rivaroxaban: 20% (3/15)	Patients dying in 1-3 days

Note: CI was not reported in any of the studies

5.2.2 Difference in change measured on mRS from baseline to after 30 days

Change measured on modified Rankin scale (mRS) was only measured for andexanet alfa in the first report of the ANNEXA-4 study by Connolly et al. (2016) [11], see Table 6. None of the studies included outcomes for PCC.

TABLE 6. RESULTS REFERRING TO DIFFERENCE IN CHANGE MEASURED ON MRS FROM BASELINE AFTER 30 DAYS

Results per treatment	Studies included in the analysis	Treatment	N	Estimate	Methods used for quantitative synthesis
Andexanet alfa	Connolly et al. (2016) [11]	Andexanet alfa	28 patients with ICH evaluated	2.2±1.9 at baseline and 2.0±2 0 among the survivors	Patients with intracranial bleeding were evaluated at baseline with the use of the modified Rankin scale for global disability and handicap, with scores ranging from 0 (no symptoms or disability) to 6 (death).

Note: CI was not reported in the study

5.2.3 Proportion of patients who achieve effective haemostasis within 48 hours

The protocol stated that effective haemostasis should be measured in accordance with the International Society on Thrombosis and Haemostasis (ISTH) new standardization criteria. However, in most of the studies on PCC this criterion has not been used. Therefore, the interpretation of the different outcomes will differ and are not comparable. All 4 andexanet alfa studies report efficacy within 12 hours and PCC studies report efficacy within 48 hours (1), 24 hours (5), and 8 did not report a timeframe. Table 7 presents the proportion of patients who achieve effective haemostasis within 48 hours by study.

The ANNEXA-4 study showed that clinical haemostasis was adjudicated as excellent or good by an independent adjudication committee using standardised pre-defined criteria of haemostatic efficacy in 82% of patients 12 hours after andexanet alfa infusion.[12]

In the study where the timeframe was known to be 48 hours, effectiveness of PCC in managing bleeding (defined as there being no recurrent bleeding and the patient still being alive) was estimated to be 73.75%.[8] Haemostatic effectiveness was estimated to be within a range of 65-87.5% in studies measuring effectiveness within 24 hours [14, 17, 19, 21, 23] and 66-94.4% in studies where the timeframe was not reported [5, 7, 9, 16, 20, 22, 24, 26]. Comparisons between andexanet alfa and PCC studies are hard to make as the studies have different inclusion and exclusion criteria, different sample sizes with different characteristics and different definitions of haemostasis.

TABLE 7. RESULTS REFERRING PROPORTION OF PATIENTS WHO ACHIEVE EFFECTIVE HAEMOSTASIS WITHIN 48 HOURS

Results per treatment	Studies included in the analysis	Treatment	N	Estimate	CI	Methods used for quantitative synthesis
Andexanet alfa	Brown et al. (2019) [10]	Andexanet alfa (6/22 on high dose)	11 patients with ICH evaluated	90,9%		For ICH, clinical efficacy was defined as lack of haematoma expansion. IPH expansion was defined as > 20% increase from pre-treatment haematoma volume, and subdural haematoma (SDH) expansion was defined as > 20% increase in maximal haematoma diameter. For IPH, volume was determined by the ABC/2 method.
	Connolly et al. (2016) [11]	Andexanet alfa	47 in efficacy population	Overall: 79% Low dose: 76% High dose: 100% Rivaroxaban: 81% Apixaban: 75% GI: 84% Intracranial: 80%	64-89 61-88 48-100 61-93 51-91 64-96 56-94	ICH was assessed by serial CT or MRI scans that were reviewed by an independent core laboratory; an increase volume of 35% or less from baseline at 12 hours was considered good haemostasis. Other nonvisible bleeding, including all GI bleeds, was evaluated on the basis of both the corrected haemoglobin level and haematocrit at 12 hours, as compared with baseline, with a decrease of 20% or less and with the administration of no more than two units of additional coagulation intervention (e.g., plasma or prothrombin complex concentrate) considered to be good haemostasis. In visible bleeds, a cessation of bleeding was considered to indicate haemostatic efficacy if it occurred within 4 hours and no additional coagulation intervention was required. Efficacy population included only patients in whom the baseline anti–factor Xa activity was later determined to be 75 ng per millilitre or more (or <0.5 IU per millilitre for those receiving enoxaparin) and the acute major bleeding episode was later adjudicated to meet the study criteria.
	Connolly et al. (2019) [12]	Andexanet alfa	249 in efficacy population	Overall: 82% Low dose: 83% High dose: 78% Rivaroxaban: 80% Apixaban: 83% GI: 85% Intracranial: 80% Other: 86%	77-87 78-88 65-91 72-88 77-90 68-96 78-95 74-86	Based on Connolly et al. (2016). Estimate differs slightly from what was reported in the EPAR (overall effectiveness 80.6%) because of a larger sample.
	Stevens et al. (2019) [25]	Andexanet alfa (15% on high dose, 85% on low)	13	Overall: 77% ICH: 50% Non-ICH: 88%		Based on Connolly et al. (2016) but did not consider a specific efficacy group.
PCC	Allison et al. (2018) [7]	PCC 35 U/kg	31	83,8% - achieved haemostasis		Timeframe unknown; assessed using computed tomography (CT) for radiographic imaging to evaluate bleeding progression.
	Arachchillage et al. (2019) [8]	PCC 16,7-50 U/kg (rivaroxaban; mean 26,8) and 18,5-43 U/kg (apixaban; mean 25)	40 on rivaroxaban, 40 on apixaban	Overall DOACs: 73,75% (59/80) Apixaban: 72,5% (29/40) Rivaroxaban: 75% (30/40)		Effectiveness measured in 48 h. Effectiveness of PCC in managing ICH was based on repeat computed tomography scan of the head when required, the change in the neurological status of the patients and the requirement for further doses of PCC. PCC treatment was considered effective if there was no recurrent bleeding within 48 h and if the patient was still alive
	Berger et al. (2019) [9]	PCC 25 U/kg	18 on rivaroxaban and apixaban	Overall: 94,4% (17/18) Rivaroxaban: 92,9% (13/14) Apixaban: 100% (4/4)		Timeframe unknown; measured whether bleeding ceased (does not say haemostatic effectiveness). Coagulation measurements included PT, aPTT, endogenous thrombin potential (ETP)

				Intraparenchymal haemorrhage: 83,3% 5/6 Subdural haematoma: 100% 5/5 Subarachnoid haemorrhage: 100% (7/7) Suprasellar haematoma: 100% (1/1		
	Frontera et al. (2020) [14]	PCC recommended dose was 50 U/kg	46	4F-PCC: Overall: 72% Intracranial or intraspinal haemorrhage: 69% GI: 82% Intraabdominal or intrathoracic: 67%		Haemostatic effectiveness within 24 h was evaluated using the ISTH/SSC criteria; ICH patients underwent CT scanning
	Gerner et al. (2018) [5]		103 patients received PCC; includes 9 patients on dabigatran	66% (68/103) Risk ratio: 1,15	0,632-2,090	Timeframe unknown; presented as 35 patients experiencing haematoma enlargement (defined as volume increase of >33% compared to initial imaging)
	Harrison et al. (2018) [16]	PCC recommended dose was 50 U/kg	14 on DOACs	92,8%		Timeframe unknown; does not present "haemostatic efficacy", but argues that 7,14% of patients had haemorrhagic expansion
	Majeed et al. (2017) [17]	PCC median dose 2000 IU (1500-2000) Apixaban 26.7 U/kg (22.0-29.9) Rivaroxaban 26.7 U/kg (20.8-29.4)	84	Overall: 69% (58/84) 66,7% (26/39) apixaban 71,1% (32/45) rivaroxaban ICH: 72,4% (21/29) apixaban; 73,3% (22/30) rivaroxaban GI: 60% (3/5) apixaban; 62,5% (5/8) rivaroxaban Visceral: 0% (0/2) apixaban, 33,3% (1/3) rivaroxaban Genitourinary: 50% (1/2) apixaban; 100% (2/2) rivaroxaban Musculoskeletal: 100% (1/1) apixaban; 100% (2/2) rivaroxaban		Effectiveness within 24 h. Haemostasis was evaluated continuously throughout the study (for ICH after 24 hours). Based on communication letter from the ISTH/SSC. For non-ICH bleeding, data were collected on changes in the haemoglobin level, the need for transfusion of blood products, the need for intervention or surgery to stop the bleeding, and the administration of other haemostatic agents before or after PCCs. For ICH, follow-up computed tomography (CT) within 24 hours, when available, was compared with the initial CT when available
	Santibanez et al. (2018) [19]	PCC 88,1% of DOAC patients received 25 U/kg	36 DOAC-related MBs; includes 4 patients on dabigatran	81,3%		Effectiveness within 24 h. In ICH bleeds, haemostatic effectiveness was achieved if the first neuroimaging result within 24 h showed no change or an improvement in haematoma volume. For other types of major bleed, haemostatic effectiveness was achieved if haemoglobin did not decrease by >20% from baseline within 24 h
	Schenk et al. (2018)	PCC 25 U/kg	13	77%		Timeframe unknown; measured whether bleeding ceased (does not say haemostatic effectiveness). Coagulation measurements included PT, aPTT, endogenous thrombin potential (ETP), thromboelastometry (ROTEM®), single factor concentrations, blood cell count and the rivaroxaban level
	Schulman et al. (2018) [20]	PCC 2000 IU	66	Overall: 65% (68% in a post hoc analysis according to the ISTH recommendation from 2016) ICH: 67% GI: 69%		Haemostatic effectiveness within 24h, treating physician was presented with all haemoglobin results, transfusions, reports from invasive procedures, and from imaging diagnostics, as well as an assessment guide (Sarode et al., i.e. the ISTH/SSC) within 7 days of treatment

	Sheikh-Taha (2019) [22]	PCC 50 U/kg	29	Overall: 72,4% Apixaban: 53,8% Rivaroxaban: 87,5% By bleed: ICH: 61,1% GI, Nose, Genitourinary Musculoskeletal: 100%		Timeframe unknown; assessed using the ISTH/SSC criteria
	Sin et al. (2016) [23]	PCC recommended dose was 25 U/kg	9 apixaban/rivaroxaban-related MBs	Overall DOAC: 87,5% (7/8) Rivaroxaban: 100% (5/5) Apixaban: 66,7% (2/3)		Effectiveness within 24 h; 1 rivaroxaban-related MB was not evaluable ICH: haemostatic effectiveness achieved if the first neuroimaging result showed unchanged or improved bleed Other bleeds: haemostatic effectiveness achieved if haemoglobin levels did not drop more than 20% from baseline within 24 hours.
	Smith et al. (2019) [24]	PCC 38,7% received 25 U/kg; 51,6% received 50 U/kg	31	80,6%		Timeframe unknown. Assessed using criteria by ISTH/SSC
	Tao et al. (2018) [26]	PCC mainly 25-50 U/kg	43	93,1% (presented as "6,9% continued to have active bleeding after receiving 4F-PCC")		Timeframe unknown; haemostatic effectiveness was determined by the treating physician based on clinical measures including haemodynamic, trend of haemoglobin and haematocrit, and active bleeding as seen on imaging or invasive procedures.

5.2.4 Proportion of patients who develop a thromboembolic event within 30 days

According to the protocol written by the DMC, the proportion of patients who develop a thromboembolic event within 30 days is a relevant outcome. The results presented below in Table 8 also includes thromboembolic events measured with other follow-up periods. All andexanet alfa studies report thromboembolic events within 30 days and PCC studies report thromboembolic event within 30 days (6), 15 days (1), 14 days (4) and in-hospital events (6; 1 also had a 6-month follow-up). The comparison for the rate of thromboembolic events within 30 days is biased into disadvantage compared to shorter periods, as thromboembolic events occurring between the specified timeframe and day 30 are not captured. Furthermore, definitions of thromboembolic events differ between studies.

In the final report of the ANNEXA-4 study, 10% of patients had a thromboembolic event during the 30-day follow-up period. A majority of events occurred in patients in whom resumption of oral anticoagulation was delayed or in patients who did not restart anticoagulation.[29] Earlier interim results (Connolly, 2016[11]) presented with higher TE rates as patients were not reanticoagulated as frequently. The same pattern can be seen in the study by Stevens et al. (2019) [24]; in this study, most of the patients included would have been excluded using the ANNEXA-4 inclusion and exclusion criteria due to low GCS scores, administration of rFVII or PCC. Among the five TEs occurring, four happened prior to reinstatement of therapeutic anticoagulation.

In PCC studies reporting thromboembolic events within 30 days, estimates ranged from 0-14% [8, 14, 16, 17, 20, 21]; as could be expected, the range was narrower when measured within 14-15 days, ranging between 0-9.1% [9, 19, 23, 26, 27], and in-hospital, ranging between 0-5.6%[7, 13, 15, 22, 24, 28].

TABLE 8. RESULTS REFERRING TO PROPORTION OF PATIENTS WHO DEVELOP A THROMBOEMBOLIC EVENT WITHIN 30 DAYS

Results per treatment	Studies included in the analysis	Treatment	N	Estimate	Methods used for quantitative synthesis
Andexanet alfa	Brown et al. (2019) [10]	Andexanet alfa (6/22 on high dose)	20 DOAC related-MBs	0%	30-day follow-up. Thrombotic events were defined as a new DVT, PE, stroke and acute coronary syndrome (ACS) among survivors after treatment per review of the medical record.
	Connolly et al. (2016) [11]	Andexanet alfa	67	18% (12/67) ICH: 21,4% (6/28) GI: 6% (2/33) Other: 67% (4/6)	All adverse events were collected throughout the 30-day study period. Thrombotic events were adjudicated according to prespecified criteria
	Connolly et al. (2019) [12]	Andexanet alfa	352	10%	All adverse events were collected throughout the 30-day study period.
	Stevens et al. (2019) [25]	Andexanet alfa (15% on high dose, 85% on low)	13	31%	Events included deep vein thrombosis, ischemic stroke, pulmonary embolism, myocardial infarction, and superficial venous thrombosis
PCC	Allison et al. (2018) [7]	PCC 35 U/kg	31	0%	In-hospital TEs; no TEs were attributable to 4-factor PCC; however, no routine imaging studies were done unless clinically indicated.
	Arachchillage et al. (2019) [8]	PCC 16,7-50 U/kg (rivaroxaban; mean 26,8) and 18,5-43 U/kg (apixaban; mean 25)	40 on apixaban, 40 on rivaroxaban	Overall: 3,75% (3/80) Apixaban: 2,5% (1/40) Rivaroxaban: 5% (2/40) By bleed: GI: 4,8% (1/21) of patients on apixaban with GI; 8% (2/25) of patients on rivaroxaban	TEs within 30 days including occurrence of an objectively verified arterial (stroke, MI, or arterial thromboembolism) or VTE (DVT or PE)

				Musculoskeletal: 0% (0/1) related to apixaban/rivaroxaban ICH: 0% (0/2) related to apixaban/rivaroxaban Visceral: 0% (0/4) related to apixaban/rivaroxaban	
	Berger et al. (2019) [9]	PCC 25 U/kg	22	Overall: 9,1% Rivaroxaban: 6,7% Apixaban: 20%	Occurrence measured within 14 days; included upper and lower extremity DVT, PE, ischemic stroke, MI, line-associated thrombosis and any other documented thromboses. All events were confirmed with reliable radiological imaging techniques and laboratory markers as appropriate (Doppler ultrasound, computed tomography pulmonary angiography, neuroimaging, electrocardiogram)
	Dybdahl et al. (2019) [13]	PCC recommended dose was 50 U/kg	62	2,9%	In-hospital TEs including DVT, stroke, PE, MI or TIA
	Frontera et al. (2020) [14]	PCC recommended dose was 50 U/kg	46	4%	TEs within 30 days were considered and included DVT, PE, cerebral infarct, MI or peripheral arterial occlusion. 4% of patients had missing values
	Grandhi et al. (2015) [15]	PCC median dose 3177 IU (2124-4770)	18	5,6%	In-hospital TEs including DVT, PE or MI
	Harrison et al. (2018) [16]	Recommended dose was 50 U/kg	14 on DOAC	0%	TEs within 30 days included were MI, DVT, PE and ischemic stroke
	Majeed et al. (2017) [17]	PCC median dose 2000 IU (1500-2000) Apixaban 26.7 U/kg (22.0-29 9) Rivaroxaban 26.7 U/kg (20.8-29.4)	84	3,6%	TEs within 30 days including objectively verified arterial (stroke, MI, arterial TE) or venous TE (DVT or PE); judged by an independent event adjudication committee
	Santibanez et al. (2018) [19]	PCC 88,1% of DOAC patients received 25 U/kg	36 DOAC-related MBs	5,6%	TEs within 14 days, including upper and lower extremity DVT, PE, ischemic stroke, MI, line-associated thrombosis, and any other documented thrombosis. Events were confirmed with reliable radiological imaging techniques and laboratory markers. DVT was confirmed by Doppler ultrasound, PE by computed tomography pulmonary angiography, ischemic stroke by neuroimaging, MI by electrocardiogram and troponin elevation, line-associated thrombosis by Doppler ultrasound with documentation of indwelling venous catheters or evidence of upper extremity catheter at the site of thrombosis within 7 days of thrombosis detection, and other thromboses by reliable radiographic imaging modalities.
	Schenk et al. (2018) [20]	PCC 25 U/kg	13	14%	Measured within 30 days; evaluated by thrombotic screening via duplex ultrasound
	Schulman et al. (2018) [21]	PCC 2000 IU	66	8%	Study team performed follow-up after 30 +/- 2 days; TEs were defined as symptomatic DVT, PE, ischaemic stroke, heart valve or cardiac chamber thrombosis, symptomatic peripheral arterial thrombosis or MI
	Sheikh-Taha (2019) [22]	PCC 50 U/kg	29	Overall: 3,4% Apixaban: 7,7% (1/13) ICH: 4,7% (1/21)	In-hospital TEs; one patient treated with apixaban who had ICH experienced a TE. TEs included MI, stroke, TIA, DVT, and PE
	Sin et al. (2016) [23]	PCC recommended dose was 25 U/kg	9 apixaban/rivaroxaban-related MBs	Rivaroxaban: 0% Apixaban: 0%	Prevalence of TEs within 14 days was based on diagnostic imaging or tests and physician notes. TEs included MI, DVT, PE and other venous or arterial TEs and were confirmed by electrodiagram, neuroimaging, Doppler ultrasound, tomography pulmonary angiography and other reliable imaging techniques
	Smith et al. (2019) [24]	PCC 38,7% received 25 U/kg; 51,6% received 50 U/kg	31	0%	In-hospital TEs. Arterial or venous thromboembolism
	Tao et al. (2018) [26]	PCC mainly 25-50 U/kg	43	Overall: 2,1% (1/43) Rivaroxaban: 4,8% (1/21) ICH: 6,25% (1/16)	TEs were measured within 14 days; 1 additional within 3 months who received apixaban and had GI bleed. TEs were defined as acute DVT, PE, MI or acute coronary syndrome, transient ischemic stroke, cerebral vascular accidents, and arterial thrombosis of limb or mesentery
	Tellor et al. (2018) [27]	PCC 50 U/kg, 25 U/kg or 10 U/kg;	27 DOAC-related MBs	3,7% (1/27)	TEs within 15 days

		recommended was 50			
	Testa et al. (2018) [28]	PCC – dose unknown	5 on apixaban and 15 on rivaroxaban treated with PCC	0%	No in-hospital TEs; however, 4 patients experienced TEs at the 6 month follow up, none of them had been treated with PCC

Note: CI was not reported in any of the studies

5.2.5 Qualitative review of adverse reaction profile and safety aspects

Table 9 provides information of adverse reaction profile and safety aspects as described in the different studies.

In the ANNEXA-4 trial, 34 patients (10%) had a thrombotic event within the 30-day follow-up period. Myocardial infarction occurred in 7 patients, ischemic stroke in 14, deep-vein thrombosis in 13, and pulmonary embolus in 5. There were 2 patients with infusion-related reactions, neither of which was severe. Antibodies to factor X or Xa did not develop in any patients after andexanet treatment, and no neutralizing antibodies to andexanet developed.[12]

The qualitative review of adverse reaction profile and safety among PCC is more heterogenous and, as such, only presented in Table 9.

TABLE 9. RESULTS REFERRING TO QUALITATIVE REVIEW OF ADVERSE REACTION PROFILE AND SAFETY ASPECTS

Results per treatment	Studies included in the analysis	Treatment	N	Review
Andexanet alfa	Connolly et al. (2016) [11]	Andexanet alfa	67	No infusion reactions; no antibodies to FXa or FX; no neutralizing antibodies to andexanet alfa; TEs in 12 patients (18%) with some patients having more than one event; 10 deaths (15%); 18 patients (27%) restarted anticoagulation within 30 days
	Connolly et al. (2019) [12]	Andexanet alfa	352	34 (10%) of patients had a TE during the 30-day follow-up (7 MI, 14 ischemic strokes, 1 TIA, 13 DVT 5 PE); 2 infusion reactions (non-severe); no antibodies to FXa or FX; no neutralizing antibodies to andexanet alfa; 49 patients (14%) died within 30 days after enrolment (35 of cardiovascular causes, 12 of non-cardiovascular causes, and 2 of unknown causes); 100 patients (28%) were restarted on oral anticoagulation during follow-up
	Stevens et al. (2019) [25]	Andexanet alfa (15% on high dose, 85% on low)	13	4 (31%) patients experienced 5 TEs within 30 days after treatment (the median time to event was 6.5 days [IQR: 1-26 days]) including DVT, ischemic stroke, PE, MI, and superficial venous thrombosis (2/4 patients who had a TE were also treated with FVIIa and/or 4F-PCC); 8 patients were not restarted on anticoagulation during their hospital admission; the median time to initiation of anticoagulation (among those patients who were restarted) after bleed was 4 5 days (IQR: 2-5.5 days); 2 (15%) of patients died within 30 days after treatment (median time to event was 2 days [range: 1.5-2.5]), both patients had an ICH with a Glasgow Coma Score (GCS) of 8 and 4, respectively. No patients in the non-ICH group died
PCC	Allison et al. (2018) [7]	PCC 35 U/kg	31	No TEs reported were attributable to 4F-PCC; however, no routine imaging studies were done unless clinically indicated. 5/33 died (care was withdrawn in 3, 1 died from pneumonia and 1 from multi-organ failure)
	Arachchillage et al. (2019) [8]	PCC 16,7-50 U/kg (rivaroxaban; mean 26,8) and 18,5-43 U/kg (apixaban; mean 25)	40 on apixaban, 40 on rivaroxaban	Recurrent bleeding within 48h was 17,5% and 27,5% for patients on rivaroxaban and apixaban, respectively (20% and 15% in ICH patients; recurrent ICH bleeding was 12% and 9,5%); recurrent bleeding within 30 days was 20% and 30,8% for rivaroxaban and apixaban, respectively; anticoagulation was restarted in 25% and 32,5% patients on rivaroxaban and apixaban, respectively (16% and 19% in ICH patients)
	Berger et al. (2019) [9]	PCC 25 U/kg	22	One patient developed an ischemic stroke 0.5 days after 4F-PCC; the second patient developed a left lower extremity DVT 7.3 days after 4F-PCC. Among patients who died, 2 were transitioned to withdrawal of care, and the other 2 experienced a cardiac arrest.
	Dybdahl et al. (2019) [13]	PCC recommended dose was 50 U/kg	62	The no reversal group had a significantly higher incidence of ischemic stroke or TIA than the 4F-PCC group (4F-PCC: 0%; no reversal: 14.8%). There was no difference in the incidence of VTE or MI between the two groups. After controlling for ISS, there was no significant difference in mortality, ICU length of stay, or ischemic stroke or TIA.
	Frontera et al. (2020) [14]	PCC recommended	46	TEs consisted of one patient with acute ischemic stroke and one with DVT. 50% of patients had a good discharge disposition and the overall median length of stay was 5 days

		dose was 50 U/kg		
	Grandhi et al. (2015) [15]	PCC median dose 3177 IU (2124-4770)	18	The overall in-hospital mortality rate was 33%; families withdrew care on 4 patients, and 2 patients on apixaban expired due to respiratory failure secondary to aspiration pneumonia with no evidence of haemorrhage progression on head CT
	Harrison et al. (2018) [16]	PCC recommended dose was 50 U/kg	14 on DOAC	Mortality and outcome data and lack of VTE complications suggest that 4F-PCC is unlikely to worsen outcomes with factor Xa inhibitor–associated ICH but the findings suggest no clear evidence of benefit or harm with 4F-PCC for patients with factor Xa inhibitor–associated ICH.
	Majeed et al. (2017) [17]	PCC median dose 2000 IU (1500-2000) Apixaban 26.7 U/kg (22.0-29.9) Rivaroxaban 26.7 U/kg (20.8-29.4)	84	The only adverse events reported are TEs. 1 ICH patient on apixaban died from stroke and 1 ICH patient on rivaroxaban died from suspected PE 18 days after treatment. Among 27 deaths within 30 days, the cause of death was due to the direct effect of the bleeding in 66.7% of patients, sepsis and multiorgan failure In 25.9%, and cardiac arrhythmia and arrest in 1 patient each (3.7%).
	Schenk et al. (2018) [20]	PCC 25 U/kg	13	3 died (septic shock (1), progressive cancer (1) and ICH (1)). All deaths were considered to be unrelated to the study medication; 3/13 patients showed signs of re-bleeding (progressive ICH) after administration of PCC; other serious adverse events were an epileptic event, ischemia caused by thromboembolic closure of the femoral artery bifurcation, sepsis and embolic arteria cerebri anterior infarct (one patient).
	Schulman et al. (2018) [21]	PCC 2000 IU	66	6 TEs were diagnosed 1, 2, 9, 12 and 22 (2) days after PCC; 9 (14%) patients died whereof 8 had ICH (22% of the intracranial bleeds), 7 of the deaths were adjudicated as 'a result of the index (intracranial) bleeding event'. 1 death was in a patient with self-inflicted stab wounds to the chest. There were 8 additional serious adverse events, all among patients with initial ICH; 6 with prolonged hospitalization due to extracranial bleeding (GI 1; gross haematuria—2), and 1 patient each with cellulitis, infection + hypernatremia + delirium, neurological deterioration due to expansion of previously evacuated subdural haematoma; and two with re-hospitalizations for gastrointestinal bleeding)
	Sheikh-Taha (2019) [22]	PCC 50 U/kg	29	8 (27.6%) failed to achieve haemostasis, all of them suffered from ICH (6 died during hospitalization and 2 suffered from neurologic deterioration upon hospital discharge).
	Sin et al. (2016) [23]	PCC recommended dose was 25 U/kg	9 apixaban/rivaroxaban-related MBs	The single patient treated with FXa inhibitor that experienced a TE was treated pre surgery; no other safety parameters presented separately for FXa inhibitor patients
	Tao et al. (2018) [26]	PCC mainly 25-50 U/kg	43	3 patients continued to bleed after treatment with 4F-PCC, whereof 2 died from haemorrhage; 1 TE (upper extremity DVT) occurred in a patient on rivaroxaban who had ICH (1 day after treatment with PCC)
	Tellor et al. (2018) [27]	PCC 50 U/kg, 25 U/kg or 10 U/kg; recommended was 50	27 DOAC-related MBs	1 person had a DVT; 6 people died (2 indicated for emergency surgery, 3 for ICH and 1 for intraperitoneal bleed). 3 deaths were not directly attributable to bleeding complications. 24/29 did not continue DOAC therapy at discharge

Note: CI was not reported in any of the studies

5.2.6 Difference in change in EQ-5D index score

No studies measuring quality of life outcomes for andexanet alfa or PCC were found.

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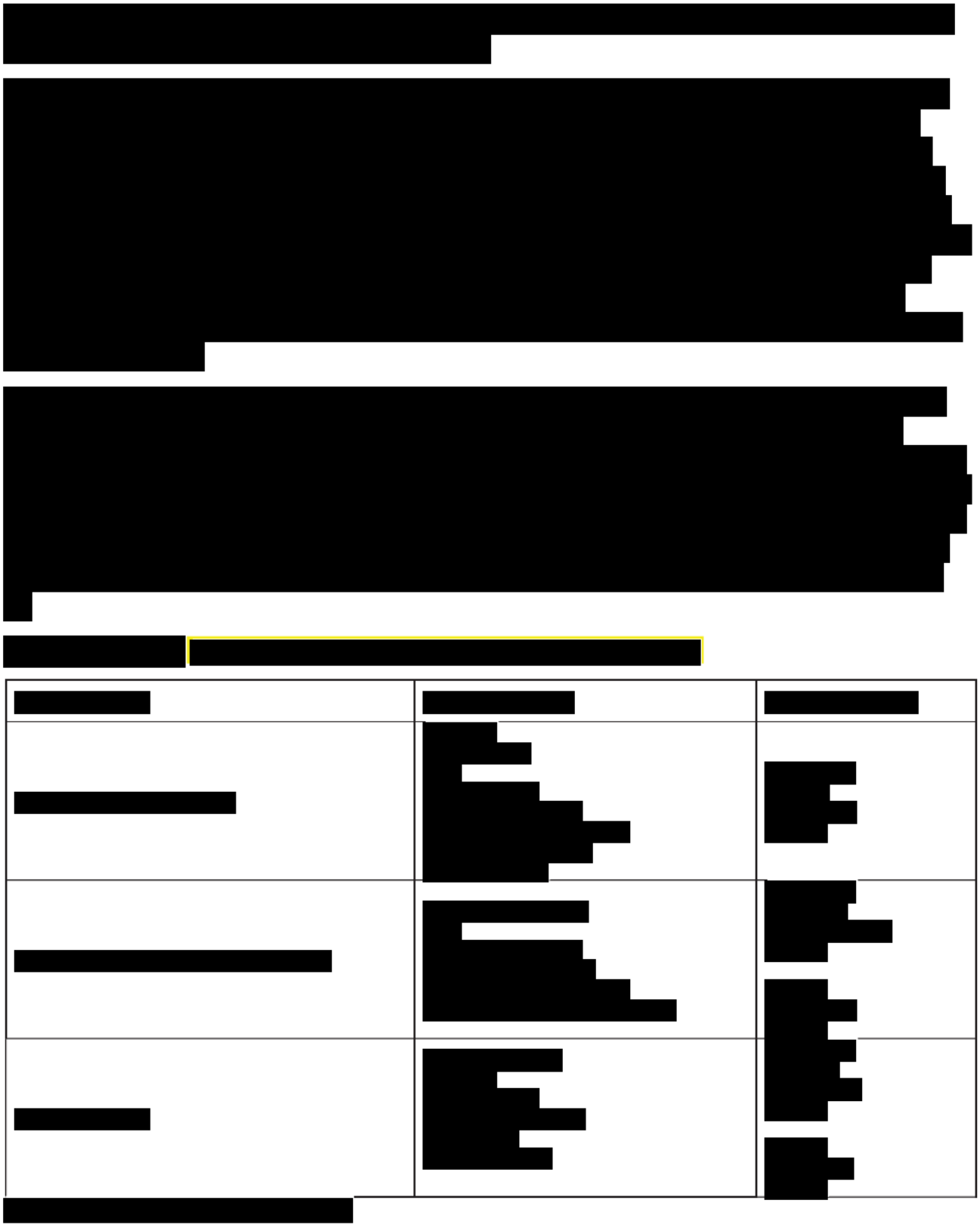

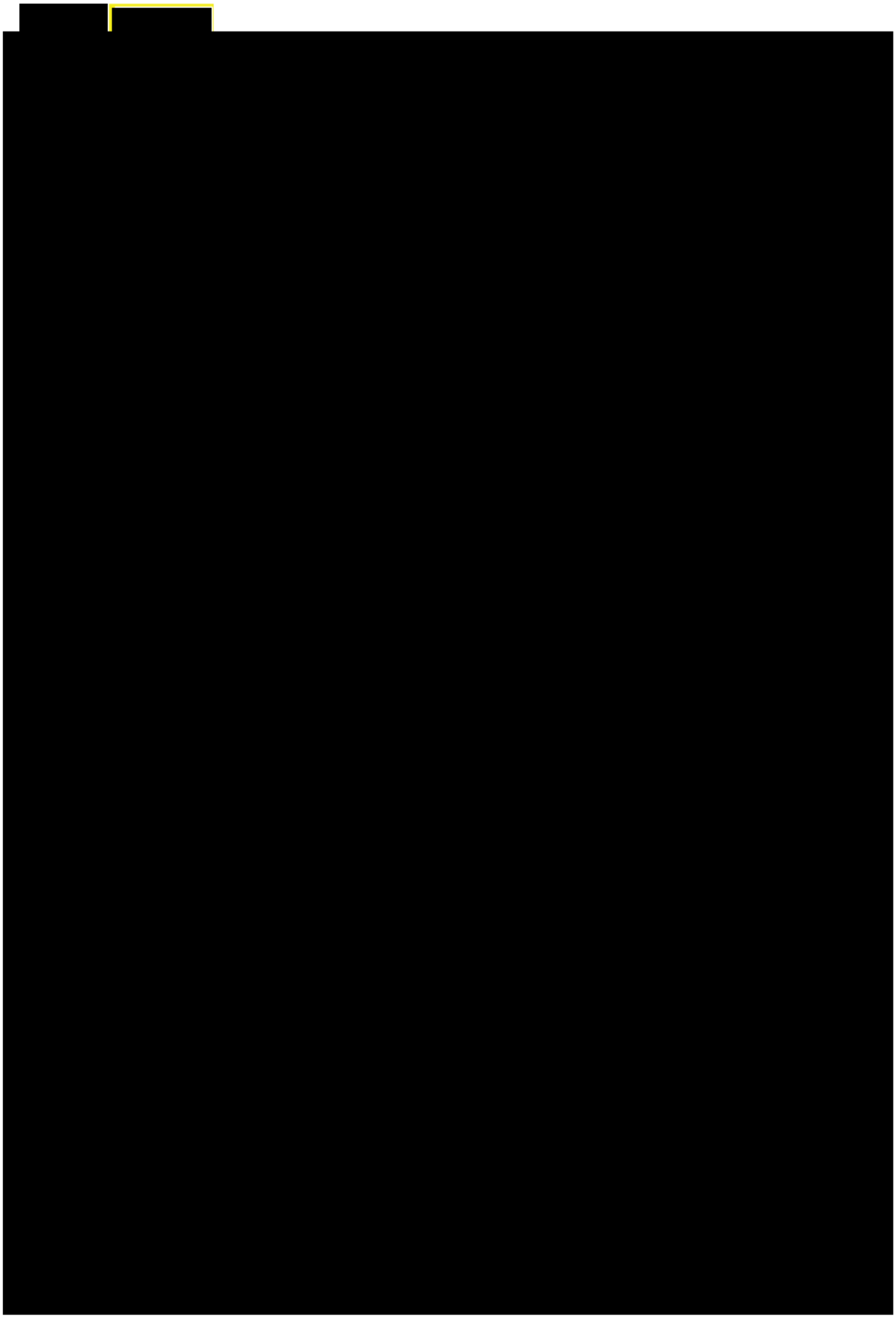

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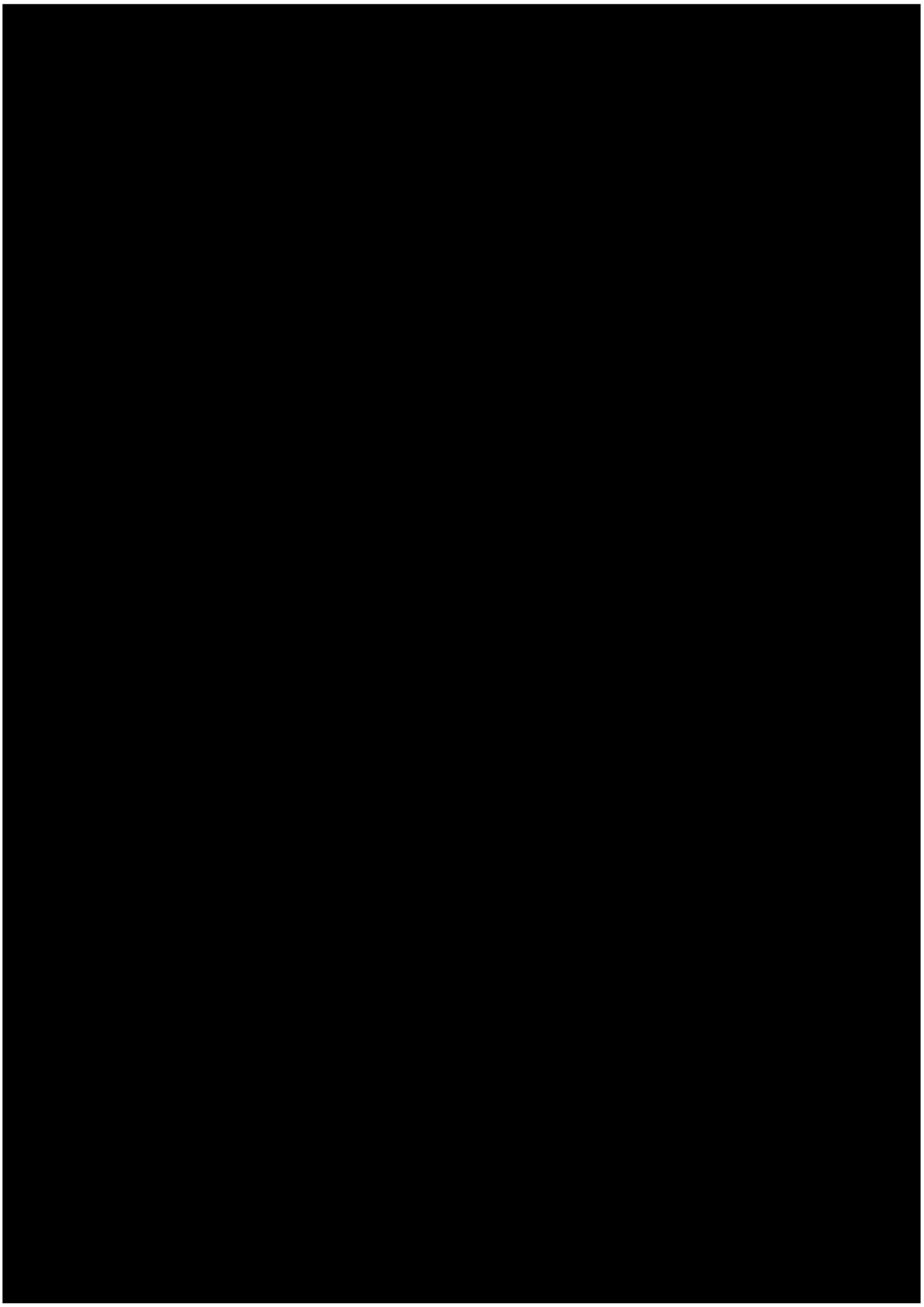

5.4 Additional studies

5.4.1 Real-world management of oral factor Xa inhibitor-related bleeds with reversal or replacement agents including andexanet alfa and four-factor prothrombin complex concentrate: a multicenter study

The study *Real-world management of oral factor Xa inhibitor-related bleeds with reversal or replacement agents including andexanet alfa and four-factor prothrombin complex concentrate: a multicenter study* by Coleman et al. (2020) was written to describe real-world utilization and outcomes associated with managing DOAC-related major bleeds. The study is a retrospective survey based on electronic medical records from 45 US-based hospitals between January 2016 and September 2019. [50]

In total, 3,030 records of patients treated with FXa inhibitors were identified whereof 342 were treated with andexanet alfa and 733 were treated with 4F-PCC. The rest of the patients were treated with fresh frozen plasma (925), other (3F-PCC, recombinant Factor VIIa, activated 4F-PCC, tranexamic acid and vitamin K [794]) or no reversal (438). Patient demographics were relatively similar across the treatments administered. Among patients administered andexanet alfa (4F-PCC), 40% (41%) had GI bleeds, 20% (23%) had ICH bleeds, 3% (29%) had bleeds in the critical compartment, 31% (4%) were traumatic bleeds and 6% (3%) were other bleeds. In 83% (72%) of cases when patients were treated with andexanet alfa (4F-PCC), it was the sole agent administered.[50]

The study measured in-hospital mortality, LOS and ICU LOS, results are presented in Table 17. Overall mortality for andexanet alfa and 4F-PCC was 4% and 10%, respectively. Patients treated with andexanet alfa had, on average, the lowest in-hospital mortality rates across all bleed types. LOS and ICU LOS was highest for the more severe bleeds (ICH and critical compartment) and ICU LOS was, on average, one day shorter for andexanet alfa compared with 4F-PCC. [50]

TABLE 17. STUDY RESULTS FOR ANDEXANET ALFA AND 4F-PCC

	Andexanet alfa			4F-PCC		
Type of bleed	**In-hospital mortality**	**Median LOS (IQR)**	**Median ICU LOS (IQR)**	**In-hospital mortality**	**Median LOS (IQR)**	**Median ICU LOS (IQR)**
All	12/342	5.0 (3.0-6.0)	2.0 (1.0-4.0)	74/733	5.0 (4.0-7.0)	3.0 (2.0-5.0)
GI	2/137	4.0 (3.0-5.0)	2.0 (1.0-2.0)	12/303	4.0 (3.0-5.0)	2.0 (1.0-3.0)
ICH	6/67	7.0 (6.0-8.0)	4.0 (3.0-6.0)	43/170	7.0 (4.0-9.0)	4.0 (3.0-6.0)
Critical compartment	0/11	7.0 (6.0-9.0)	5.0 (4.0-7.0)	1/26	5.5 (4.0-8.8)	3.0 (2.0-5.0)
Traumatic	4/105	5.0 (3.0-6.0)	2.0 (1.0-3.5)	16/214	6.0 (4.0-8.0)	3.0 (2.0-5.0)
Other*	0/22	-	-	2/20	-	-

*Results were not presented due to low sample size and variability in type of bleeds.

5.4.2 Major and Life-Threatening Bleeds ON Anticoagulation Therapy – Patient Numbers and Outcomes in Germany in 2017

The study *Major and Life-Threatening Bleeds ON Anticoagulation Therapy – Patient Numbers and Outcomes in Germany in 2017*, conducted by Altevers et al. in 2020 is a retrospective claims data analysis from the perspective of the German Statutory Health Insurance that utilized data from the Institute for Applied Health Research Berlin (InGef) Research Database. [51] This study gives a good idea of the annual rate of major and life-threatening bleeds.

The study included patients continuously enrolled between January 01, 2016 and December 31, 2017 in the InGef Research Database who were 18 years or older on January 01, 2017 and had not deceased at any point in 2017. *Major* bleeds were identified using an algorithm developed by Cunningham et al. [52], with the exception that trauma-induced bleeds were not excluded. Treatment with apixaban or rivaroxaban was identified if the admission date was within the days' supply of the apixaban/rivaroxaban prescription closest to the admission plus a wash-out phase of seven days. *Life-threatening* bleeds were identified among major bleeds, restricted to intracranial bleeds or bleeding-related hospitalizations resulting in death. The results were extrapolated to the German population. [51]

The results of the study showed that 1,400 patients on rivaroxaban or apixaban in the dataset had a major bleed, whereof 211 had life-threatening bleeds. In total, these patients had 1,575 (249) major (life-threatening) bleeds, resulting in an event rate of 1.13 (1.18) bleeds per patient. [51]

Extrapolation to the German population in 2017 showed that 31,484 (95% CI: 29,857 – 33,177) patients were estimated to have had a major bleed and 4,745 (95% CI: 4,126 – 5,430) patients were estimated to have had a life-threatening bleed among a projected population of 1,665,691 patients on therapy with apixaban/rivaroxaban. This corresponds to an annual rate of 1.9% for major bleeds and 0.3% for life-threatening bleeds among patients on apixaban/rivaroxaban in Germany in 2017. [51]

Extrapolating the results to the Danish population receiving apixaban/rivaroxaban in the second quarter of 2020 (95,576 patients) using data from Sundhedsdatastyrelsen [53] would translate to 1,816 patients having 2,052 major bleeds in Denmark annually. The corresponding numbers for life-threatening bleeds would be 287 patients experiencing 338 life-threatening bleeds in Denmark annually. [51, 53]

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7 Appendices

7.1 Literature search

TABLE A 1. INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria	Population: Patients receiving direct FXa inhibitor (apixaban and rivaroxaban) and have major bleeding Intervention(s): Andexanet alfa or PCC 25-50 IU/kg Comparator(s): Outcomes: • Proportion of patients dying within 30 days • Difference in change measured on modified Rankin scale (MRS) from baseline to after 30 days • Proportion of patients who achieve effective haemostasis within 48 hours, cf. ISTH criteria • Proportion of patients who develop a thromboembolic event within 30 days • Qualitative review of adverse reaction profile and safety aspects • Difference in change in EQ-5D index score Settings (if applicable): Study design: Language restrictions: English Other search limits or restrictions applied:
Exclusion criteria	Clinical studies with other populations than those selected and studies that do not report at least one of the critical or important endpoints.

TABLE A 2. REASONS FOR EXCLUSION AFTER FULL-TEXT REVIEW

Reference	Reason for exclusion
Albaladejo, P., et al. (2017) [54]	No relevant endpoint assessed
Barzilai, M., et al. (2019) [55]	Irrelevant patient group studied
Beynon, C., et al. (2015) [56]	No relevant endpoint assessed
Favresse, J., et al. (2019) [57]	Review of earlier studies
Green, L., et al. (2019) [45]	No relevant endpoint assessed
Hedges, A., et al. (2016) [58]	No relevant endpoint assessed
Herrmann, R., et al. (2014) [59]	No relevant endpoint assessed
Karli, B., et al. (2015) [60]	No relevant endpoint assessed
Marcos-Jubilar, M., et al. (2019) [61]	Irrelevant patient group studied
Nafee, T., et al. (2017) [62]	Review of earlier studies
Piran, S., et al. (2018) [63]	Irrelevant patient group studied
Purrucker, J., et al. (2016) [64]	No relevant endpoint assessed
Siegal, D., et al. (2017) [65]	Irrelevant patient group studied
Siegal, D.M., et al. (2015) [66]	Irrelevant patient group studied
Won, S.Y., et al. (2017) [67]	No relevant endpoint assessed
Yoshimura, S., et al. (2017) [68]	Irrelevant patient group studied
Zada, L., et al. (2019) [69]	Irrelevant patient group studied

7.2 Main characteristics of included studies

TABLE A 3. MAIN CHARACTERISTICS OF INCLUDED STUDIES

Trial name	*Real-world utilization of andexanet alfa*
NCT number	*NCT02329327*
Objective	*To describe real world utilization of andexanet alfa.*
Publications – title, author, journal, year	*Brown, C.S., et al., Real-world utilization of andexanet alfa. Am J Emerg Med, 2019.[10]*
Study type and design	*Retrospective observational case study*
Follow-up time	*30 days*
Population (inclusion and exclusion criteria)	*Inclusion criteria:* • *Patients receiving andexanet alfa for reversal of DOACs due to MBs or prior to procedures at Mayo Clinic (n=30)* *Exclusion criteria:* • *5 patients excluded due to declining authorisation for use of medical records*
Intervention	*Andexanet alfa* • *27% (6/22) of patients treated for reversal due to DOAC-related MBs had high doses* • *73% (16/22) patients treated for reversal due to DOAC-related MBs had low doses* *See Connolly et al. (2016) for definition of high and low dose*
Baseline characteristics	*N=25* • *Median age: 75 years (IQR 71-83)* • *60% (15/25) female* • *80% anticoagulated with apixaban and 20% with rivaroxaban* • *60% were on DOACs for AF* • *3 patients had a documented history of a bleed and 4 had surgery in the previous year* • *Median LOS was 4 days (IQR 3-6)* • *52% (13) were treated for ICH; 36% (9) for bleeding at other sites (including GI; n=4); 12% (3) for reversal of anticoagulation before procedures* *Results presented in this review only includes the 22 who were treated for MB*
Primary and secondary endpoints	*Primary endpoints: stability of haematoma for intracranial haemorrhage (ICH); haemostatic effectiveness for patients undergoing surgical procedures* *Secondary endpoints: thromboembolism; 30-day mortality*
Method of analysis	*Data is presented as median with interquartile range (IQR)*
Subgroup analyses	*Subgroup analyses were made for type of DOAC and type of bleed using the same methods as for the baseline analysis*

Trial name	*ANNEXA-4*
NCT number	*NCT02329327*
Objective	*To evaluate efficacy and safety of andexanet alfa in patients receiving a FXa inhibitor (apixaban, rivaroxaban, edoxaban, or enoxaparin) with acute MB*
Publications – title, author, journal, year	*Connolly, S.J., et al., Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. N Engl J Med, 2016. 375(12): p. 1131-41.[11]*
Study type and design	*Phase 3 - multicenter, prospective, open-label, single-group study*

Follow-up time	*30 days*
Population (inclusion and exclusion criteria)	*Inclusion:* 1. *Acute major bleeding episode requiring urgent reversal of anticoagulation; defined by at least one of the following:* • *Acute bleeding that is potentially life-threatening, OR* • *Acute bleeding associated with a fall in haemoglobin level by ≥2 g/dL, OR* • *Acute bleeding associated waith a haemoglobin level of ≤8 g/dL if no baseline haemoglobin is available, OR* • *Acute bleeding in a critical area or organ such as intraspinal, pericardial, or intracranial.* 2. *If bleeding is intracranial or intraspinal, the patient must have undergone a head CT or MRI scan demonstrating the bleeding.* 3. *Patient received or is believed to have received one of the following within 18 hours prior to andexanet administration: apixaban, rivaroxaban, edoxaban or enoxaparin.* 4. *For patients with intracranial bleeding, there must be a reasonable expectation that andexanet treatment will commence within 2 hours of the baseline imaging evaluation.* *Exclusion:* 1. *The patient is scheduled to undergo surgery in less than 12 hours, with the exception of minimally invasive surgery/procedures.* 2. *A patient with an intracerebral haemorrhage has any of the following:* • *Glasgow coma score < 7, OR* • *Intracerebral haematoma > 60 cc as assessed by CT or MRI* 3. *Patients with visible, musculoskeletal or intra-articular bleeding as their qualifying bleed.* 4. *Expected survival of less than 1 month* 5. *Recent history (within 2 weeks) of a diagnosed thrombotic event (TE) as follows: venous thromboembolism, myocardial infarction, disseminated intravascular coagulation (DIC), cerebral vascular accident, transient ischemic attack, unstable angina pectoris hospitalization or severe peripheral vascular disease within 2 weeks prior to screening.* 6. *Severe sepsis or septic shock at the time of Screening.* 7. *Pregnant or a lactating female.* 8. *Patient has received any of the following drugs or blood products within 7 days of Screening:* • *Vitamin K antagonist (VKA)* • *Dabigatran* • *Prothrombin Complex Concentrate products (PCC) or recombinant factor VIIa (rfVIIa)* • *Whole blood, plasma fractions* • *Treated with an investigational drug <30 days prior to Screening* *Planned administration of PCC, fresh frozen plasma (FFP) or rfVIIa from Screening until within 12 hours after the end of the andexanet infusion.*
Intervention	*Andexanet alfa* *Patients received a bolus during a period of 15 to 30 minutes, followed by a 2-hour infusion. For patients who had taken apixaban or rivaroxaban more than 7 hours before the administration of andexanet, the bolus dose was 400 mg and the infusion dose was 480 mg (low dose). For patients who had taken enoxaparin, edoxaban, or rivaroxaban 7 hours or less before the administration of the bolus dose or at an unknown time, the bolus dose was 800 mg and the infusion dose was 960 mg (high dose). The share of patients receiving high/low dose is not reported*
Baseline characteristics	*N=67* • *Mean age: 77,1 (+/- 10) years* • *48% (25) female* • *BMI 28,1 (+/- 6,3)* • *48% (32) received rivaroxaban; 46% (31) apixaban; 6% (4) enoxaparin* • *Indication for anticoagulation: 70% AF; 22% VT; 7% AF + VT* • *Medical history: 19% MI; 25% stroke; 30% DVT; 9% PE; 73% AF; 34% heart failure; 34% diabetes mellitus* • *49% had GI bleeds; 42% ICH; 9% other bleeding sites* • *20 patients were included in the safety population but not in the efficacy population*
Primary and secondary endpoints	*Primary outcomes:% change in anti-FXa activity; rate of excellent/good haemostasis within 12 h* *Safety outcomes: thromboembolic events; 30-day mortality*
Method of analysis	*Data are reported as means (±SD) or medians and interquartile ranges for continuous variables and frequencies for categorical variables. We computed the percent change from baseline with a two-sided nonparametric confidence interval for the median.10 The rate of effective haemostasis is presented with an exact 95% confidence interval, as calculated with the use of the binomial test.*

Subgroup analyses	*Efficacy (primary) outcomes were assessed using an efficacy population (n=47) with:* • *Mean age 77,1 (+/- 10,1) years* • *49% (23) female* • *BMI 28,8 (+/- 6,7)* • *Type of DOAC: 55% rivaroxaban; 43% apixaban; 2% enoxaparin* • *Indication for anticoagulation: 68% AF; 26% VT; 6% AF + VT* • *Medical history: 15% MI; 32% stroke; 34% DVT; 9% PE; 72% AF; 40% heart failure; 36% diabetes mellitus* • *53% had GI bleeds; 43% ICH; 4% other bleeding sites* *Subgroup analyses were made for type of DOAC and type of bleed using the same methods as for the baseline analysis*

Trial name	*ANNEXA-4*
NCT number	*NCT02329327*
Objective	*To evaluate efficacy and safety of andexanet alfa in patients receiving a FXa inhibitor (apixaban, rivaroxaban, edoxaban, or enoxaparin) with acute MB*
Publications – title, author, journal, year	*Connolly, S.J., et al., Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med, 2019. 380(14): p. 1326-1335.[12]*
Study type and design	*Phase 3b/4 - multicenter, prospective, open-label, single-group study*
Follow-up time	*30 days*
Population (inclusion and exclusion criteria)	*Inclusion:* 1. *Acute major bleeding episode requiring urgent reversal of anticoagulation; defined by at least one of the following:* • *Acute bleeding that is potentially life-threatening, OR* • *Acute bleeding associated with a fall in haemoglobin level by ≥2 g/dL, OR* • *Acute bleeding associated with a haemoglobin level of ≤8 g/dL if no baseline haemoglobin is available, OR* • *Acute bleeding in a critical area or organ such as intraspinal, pericardial, or intracranial.* 2. *If bleeding is intracranial or intraspinal, the patient must have undergone a head CT or MRI scan demonstrating the bleeding.* 3. *Patient received or is believed to have received one of the following within 18 hours prior to andexanet administration: apixaban, rivaroxaban, edoxaban or enoxaparin.* 4. *For patients with intracranial bleeding, there must be a reasonable expectation that andexanet treatment will commence within 2 hours of the baseline imaging evaluation.* *Exclusion:* 1. *The patient is scheduled to undergo surgery in less than 12 hours, with the exception of minimally invasive surgery/procedures.* 2. *A patient with an intracerebral haemorrhage has any of the following:* • *Glasgow coma score < 7, OR* • *Intracerebral haematoma > 60 cc as assessed by CT or MRI* 3. *Patients with visible, musculoskeletal or intra-articular bleeding as their qualifying bleed.* 4. *Expected survival of less than 1 month* 5. *Recent history (within 2 weeks) of a diagnosed thrombotic event (TE) as follows: venous thromboembolism, myocardial infarction, disseminated intravascular coagulation (DIC), cerebral vascular accident, transient ischemic attack, unstable angina pectoris hospitalization or severe peripheral vascular disease within 2 weeks prior to screening.* 6. *Severe sepsis or septic shock at the time of Screening.* 7. *Pregnant or a lactating female.* 8. *Patient has received any of the following drugs or blood products within 7 days of Screening:* • *Vitamin K antagonist (VKA)* • *Dabigatran* • *Prothrombin Complex Concentrate products (PCC) or recombinant factor VIIa (rfVIIa)* • *Whole blood, plasma fractions* • *Treated with an investigational drug <30 days prior to Screening*

	• *Planned administration of PCC, fresh frozen plasma (FFP) or rfVIIa from Screening until within 12 hours after the end of the andexanet infusion.*
Intervention	*Andexanet alfa* *Patients received a bolus during a period of 15 to 30 minutes, followed by a 2-hour infusion. For patients who had taken apixaban or rivaroxaban more than 7 hours before the administration of andexanet, the bolus dose was 400 mg and the infusion dose was 480 mg (low dose). For patients who are believed to have taken an Fxa inhibitor but are uncertain of which one or had taken enoxaparin, edoxaban, or rivaroxaban 7 hours or less before the administration of the bolus dose or at an unknown time, the bolus dose was 800 mg and the infusion dose was 960 mg (high dose). The share of patients receiving high/low dose is not reported*
Baseline characteristics	*N=352* • *Mean age: 77,4 (+/- 10,8) years* • *47% (165) female* • *BMI 27 (+/- 5,9)* • *Type of DOAC: rivaroxaban 36%; apixaban 55%, enoxaparin 6%; edoxaban 3%* • *Indication for anticoagulation: AF 80%; VT 17%; other 3%* • *Medical history: MI 14%; stroke 20%; DVT 19%; PE 12%; AF 81%; heart failure 20%; diabetes mellitus 30%* • *Type of bleed: GI 26%; ICH 64%; other 10%* *254 patients met the criteria to join the efficacy population*
Primary and secondary endpoints	*Primary outcomes: change in anti-FXa activity; rate of excellent/good haemostasis within 12 h* *Safety outcomes: thromboembolic events; 30-day mortality*
Method of analysis	*Safety analyses included all the patients who had received andexanet. The efficacy analysis population included only patients who retrospectively met both of two criteria: baseline anti-factor Xa activity of at least 75 ng per milliliter (or ≥0.25 IU per milliliter for patients receiving enoxaparin) and confirmed major bleeding at presentation, as determined by the adjudication committee. Initially, a sample of 250 patients was planned, which would provide 80% power to show that the percentage of patients with excellent or good haemostatic efficacy was more than 50%. The sample was adjusted to 350 patients in protocol amendment 4 (January 2017) to meet new regulatory requirements for sufficient numbers of patients for each factor Xa inhibitor and to have at least 120 patients with intracranial haemorrhage in the efficacy analysis population.* *Continuous variables are summarised as mean and standard deviation or median and interquartile range; categorical variables are presented as frequencies. Percent change from baseline in anti-factor Xa activity was computed with a two-sided nonparametric confidence interval for the median. Percentages of patients with effective haemostasis are presented with a 95% confidence interval calculated with the binomial test. The association between haemostatic efficacy and change in anti-factor Xa activity was examined with the use of receiver-operating-characteristic (ROC) curves*
Subgroup analyses	*Efficacy (primary) outcomes were assessed using an efficacy population (n=254) with:* • *Mean age: 77,1 (+/- 11,1) years* • *49% (125) female* • *BMI 27 (+/- 6,2)* • *Type of DOAC: rivaroxaban 39%; apixaban 53%, enoxaparin 6%; edoxaban 2%* • *Indication for anticoagulation: AF 79%; VT 18%; other 3%* • *Medical history: MI 14%; stroke 22%; DVT 21%; PE 11%; AF 80%; heart failure 22%; diabetes mellitus 31%* • *Type of bleed: GI 24%; ICH 67%; other 8%* *Subgroup analyses were made for type of DOAC and type of bleed using the same methods as for the baseline analysis*

Trial name	*Coagulation Factor Xa (Recombinant), Inactivated-Zhzo (Andexanet Alfa) Hemostatic Outcomes and Thrombotic Event Incidence at an Academic Medical Center*
NCT number	
Objective	*Review the incidence of effective haemostasis with andexanet alfa in a real-world environment*
Publications – title, author, journal, year	*Stevens, V.M., et al., Coagulation Factor Xa (Recombinant), Inactivated-Zhzo (Andexanet Alfa) Hemostatic Outcomes and Thrombotic Event Incidence at an Academic Medical Center. Clin Appl Thromb Hemost, 2019. 25: p. 1076029619896619. [25]*
Study type and design	*Retrospective cohort study*

Follow-up time	*30 days*
Population (inclusion and exclusion criteria)	*Inclusion criteria:* • *18 years or older* • *Taking an oral FXa inhibitor* • *Presented to a University of Colorado Health System Hospital with a MB resulting in treatment with andexanet alfa in June 2018-August 2019*
Intervention	*Andexanet alfa* • *15% on high dose* • *85% on low dose* *See Connolly et al. (2016) for definition of high and low dose*
Baseline characteristics	*Descriptive statistics:* • *Mean age 69 (+/- 10) years* • *46% female* • *BMI kg/m2 32,5 (+/- 9,6)* • *Estimated creatinine clearance: <30 ml/min 15%, 30-60 ml/min 31%, >60 ml/min 54%* • *Primary indication for anticoagulation: AF 62%; VT 38%* • *Past medical history: MI 23%; stroke 0%; DVT 31%; PE 8%; heart failure 31%; diabetes mellitus 23%* • *Type of DOAC: apixaban 69%; rivaroxaban 31%* • *Type of bleed: ICH 46%; non-ICH 54%* • *Time since last FXa inhibitor dose: <8h 23%; 8-18h 46%; unknown 31%;* • *Haemodynamically unstable prior to andexanet alfa 38%*
Primary and secondary endpoints	*Primary outcome: effective haemostasis at 12 h after treatment of andexanet alfa* *Secondary outcomes: thromboembolic events after 30 days; 30-day mortality*
Method of analysis	*Categorical variables were expressed as values and percentages. Continuous variables were expressed as either mean + standard deviation or median and interquartile range. Categorical associations were analyzed using a Fisher exact test.*
Subgroup analyses	*Subgroup analysis was made based on bleeding location using the same methods as for the baseline analysis*

Trial name	*Evaluation of the Use of Low-Dose 4-Factor Prothrombin Complex Concentrate in the Reversal of Direct Oral Anticoagulants in Bleeding Patients*
NCT number	
Objective	*To assess the effectiveness of 4-factor PCC 35 U/kg and outcomes in patients admitted on direct factor Xa inhibitors requiring reversal due to major bleeding complications*
Publications – title, author, journal, year	*Allison, T.A., et al., Evaluation of the Use of Low-Dose 4-Factor Prothrombin Complex Concentrate in the Reversal of Direct Oral Anticoagulants in Bleeding Patients. J Intensive Care Med, 2018: p. 885066618800657. [7]*
Study type and design	*Observational, single-center study conducted in patients with a major bleed admitted to a level 1 trauma center*
Follow-up time	*Patients were assessed until discharge*
Population (inclusion and exclusion criteria)	*Inclusion criteria:* • *Adult patients (>=18 years)* • *Admitted to the neuroscience ICU or shock trauma ICU* • *Received FXa inhibitor* • *Presented with major bleed* *Exclusion criteria:* • *Pregnancy* • *Incarceration*
Intervention	*PCC 35 U/kg*
Baseline characteristics	*N=33 (however, 2 were later excluded):* • *Mean (SD) age 73 (14,8)*

	• *55% female* • *Type of bleed: traumatic brain injury (TBI) 39,4;, ICH 24,2%; subarachnoid haemorrhage 27,2%; GI 3%; haematoma with active extravasation 3%; intra-abdominal 3%* • *Medical history: AF 75,7%; hypertension 90,9%; hyperlipidemia 39,4%; coronary artery disease 33,3%; congestive heart failure 30,3%* • *Admission scores median (IQR): APACHE II 20 (15-26), GCS 15 (11-15)* • *18,2% required surgery* • *Type of DOAC: 81,8% rivaroxaban; 18,2% apixaban* • *Anticoagulation indication: stroke prevention in afib 72,7%; DVT or PE 18,2%, other 9,1%*
Primary and secondary endpoints	*Primary outcome: % of patients who achieved haemostasis* *Secondary outcomes: length of stay; mortality; disposition* *Safety outcomes: thromboembolic complications*
Method of analysis	*Descriptive statistics were used to evaluate the data.*
Subgroup analyses	*Subgroup analyses were made based on bleeding location and type of DOAC using the same methods as for the baseline analysis*

Trial name	*Efficacy and safety of prothrombin complex concentrate in patients treated with rivaroxaban or apixaban compared to warfarin presenting with major bleeding*
NCT number	
Objective	*Investigates the efficacy and safety of prothrombin complex concentrates (PCCs) for management of major bleeding events in patients receiving rivaroxaban, apixaban or warfarin*
Publications – title, author, journal, year	*Arachchillage, D.R.J., et al., Efficacy and safety of prothrombin complex concentrate in patients treated with rivaroxaban or apixaban compared to warfarin presenting with major bleeding. Br J Haematol, 2019. 184(5): p. 808-816. [8]*
Study type and design	*Retrospective single centre observational cohort study in a UK tertiary referral centre*
Follow-up time	*30 days*
Population (inclusion and exclusion criteria)	*Inclusion criteria:* • *Major bleeding event* • *Received apixaban, rivaroxaban or warfarin* • *Treated with PCC* *Exclusion criteria:* • *Received PCC prior to surgery/procedure*
Intervention	*PCC – dosage per DOAC:* *Rivaroxaban - mean 26,8 (range: 16,7-50) U/kg* *Apixaban - mean 25 (range: 18,5-43) U/kg*
Baseline characteristics	*N=344* *11,6% (40) on rivaroxaban; 11,6% (40) on apixaban; 77% (264) of patients were on warfarin and, as such, disregarded* *Patients on rivaroxaban:* • *Age 80,1 (SD 7,8)* • *37,5% (15) female* • *Median body weight 70 kg (range: 44-106)* • *Indication for anticoagulation: SPAF 72,5%; VTE 22,5%; AF and stroke 5%* • *Bleeding location: ICH 62,5%; GI 27,5%; visceral 5%; musculoskeletal 5%* *Patients on apixaban:* • *Age 72,5 (SD 7,9)* • *32,5% (13) female* • *Median body weight 74,7 kg (range: 40-109)* • *Indication for anticoagulation: SPAF 90%; VTE 7,5%; VTE and SPAF 2,5%* • *Bleeding location: ICH 52,5%; GI 32,5%; visceral 10%; genitourinary 2,5%; musculoskeletal 2,5%*

Primary and secondary endpoints	*Primary outcome: effective haemostasis within 48 h* *Safety outcomes: occurrence of an objectively verified arterial or venous thromboembolism*
Method of analysis	*Results were reported as number and percentage, median and range or mean with standard deviation (SD) based on the distribution of results. Groups were compared using the Chi-squared test or Fisher's Exact test for categorical data and the t-test, Mann-Whitney test, Analysis of Variance or Kruskal-Wallis test for continuous data, as appropriate.*
Subgroup analyses	*Subgroup analyses were made based on bleeding location and type of DOAC using the same methods as for the baseline analysis*

Trial name	*A Low-Dose 4F-PCC Protocol for DOAC-Associated Intracranial Hemorrhage*
NCT number	
Objective	*Evaluate the effectiveness and safety of 25 units/kg 4F-PCC for the management of DOAC-associated ICH in a real-world setting*
Publications – title, author, journal, year	*Berger, K., et al., A Low-Dose 4F-PCC Protocol for DOAC-Associated Intracranial Hemorrhage. J Intensive Care Med, 2019: p. 885066619840992. [9]*
Study type and design	*Retrospective study evaluating patients who received 4F-PCC for DOAC-associated ICH*
Follow-up time	*14 days*
Population (inclusion and exclusion criteria)	*Inclusion criteria:* • *18 years or over* • *Received at least one dose of 4F-PCC for DOAC-associated ICH* *Exclusion criteria:* • *Patients receiving 4F-PCC at an outside hospital*
Intervention	*PCC 25 U/kg*
Baseline characteristics	*N=22* • *Mean age was 79,5 (74,3-83,5)* • *50% (11) female* • *Mean weight 74,3 kg (69,1-85,2)* • *Type of DOAC: 68,2% rivaroxaban; 22,7% apixaban; 9,1% dabigatran* • *Reason for anticoagulation: AF 77,3%; VTE prophylaxis or treatment 13,6%; prosthetic valve 4,5%; cerebrovascular accident 4,5%; chronic thromboembolic pulmonary hypertension 4,5%; unknown 4,5%* • *Type of ICH: intraparenchymal haemorrhage 31,8%; subdural haematoma 31,8%; subarachnoid haemorrhage 31,8%; suprasellar haematoma 4,5%* • *Medical history: cerebrovascular accident 27,3%; upper or lower extremity DVT 22,7%; PE 4,5%*
Primary and secondary endpoints	*Primary outcome: haemostatic effectiveness within 24 h of 4F-PCC administration (no change or improvement in haematoma volume)* *Secondary outcomes: thromboembolic events within 14 days; in-hospital mortality*
Method of analysis	*Descriptive statistics were used throughout this study, with data represented as either medians (interquartile ranges) or frequencies (percentages).*
Subgroup analyses	*Subgroup analyses were made based on bleeding location and type of DOAC using the same methods as for the baseline analysis*

Trial name	*Four-factor prothrombin complex concentrate for the reversal of factor Xa inhibitors for traumatic intracranial hemorrhage*
NCT number	

Objective	*Determine the effectiveness and safety of 4F-PCC for the reversal of factor Xa inhibitors in patients with traumatic ICH*
Publications – title, author, journal, year	*Dybdahl, D., et al., Four-factor prothrombin complex concentrate for the reversal of factor Xa inhibitors for traumatic intracranial hemorrhage. Am J Emerg Med, 2019. 37(10): p. 1907-1911. [13]*
Study type and design	*Retrospective cohort study*
Follow-up time	*90 days*
Population (inclusion and exclusion criteria)	*Inclusion criteria:* • *Patients who presented with traumatic ICH (defined as an epidural haematoma, a subdural haematoma, a subarachnoid haemorrhage, or an intracerebral haemorrhage), confirmed by CT* • *Administered apixaban, rivaroxaban or edoxaban* *Exclusion criteria: not reported*
Intervention	*Recommended dose of 4F-PCC was 50 U/kg with a maximum dose of 5000 units if the INR was at least 1.5. If the INR was 1.4 or less, the guideline did not recommend administering 4F-PCC. However, the prescribing guideline allowed providers to use their clinical judgement to administer 4F-PCC outside of the guideline recommendations.*
Baseline characteristics	*N=62* • *56,4% (35) were treated with 4F-PCC; 27 had no reversal* *Among 35 patients treated with 4F-PCC:* • *Mean (SD) age 78,9 (8,86)* • *62% female* • *Initial mean (SD): GCS 13,1 (3,83), ISS 17,6 (8,89)* • *Antiplatelet use was 51,4%* • *Type of DOAC: apixaban 48,6%; rivaroxaban 51,4%* • *Anticoagulation indication: AF 85,7%; VTE 11,4%; AF and VTE 2,9%* • *Site of injury: epidural haematoma 2,9%; subdural haematoma 74,3%; subarachnoid haemorrhage 40%; intracerebral haemorrhage 34,3%; multiple 40%*
Primary and secondary endpoints	*Primary outcome: in-hospital mortality* *Secondary effectiveness outcomes: functional recovery, hospital length of stay, and ICU length of stay* *Secondary safety outcomes: in-hospital VTE, stroke or TIA and MI*
Method of analysis	*Demographic and clinical characteristics were described using mean and standard deviation for continuous variables and frequencies and percentages for binary or categorical variables. Means were compared between two independent groups using two-sample t-tests or nonparametric Wilcoxon tests. Analysis of covariance models were used to compare continuous outcomes between groups while controlling for ISS. Percentages were directly compared between two groups using chi-square tests. Logistic regression modeling was used to compare percentages while controlling for ISS*
Subgroup analyses	*Subgroups were defined a priori and subgroup analyses were performed to assess mortality based on age, gender, site of injury, antiplatelet use, and neurosurgical intervention.*

Trial name	*Cost comparison of andexanet versus prothrombin complex concentrates for direct factor Xa inhibitor reversal after hemorrhage*
NCT number	
Objective	*To project utilization rates and cost of andexanet for reversal of dFXaI-related major hemorrhage compared to 4-factor prothrombin complex concentrates (4F-PCC)*
Publications – title, author, journal, year	*Frontera, J.A., et al., Cost comparison of andexanet versus prothrombin complex concentrates for direct factor Xa inhibitor reversal after hemorrhage. J Thromb Thrombolysis, 2020. 49(1): p. 121-131. [14]*
Study type and design	*Comparatory study with a retrospective, multicenter approach when looking at 4F-PCC and published ANNEXA-4 data when looking at andexanet alfa*
Follow-up time	*30 days*
Population (inclusion and exclusion criteria)	*Inclusion criteria (based on ANNEXA-4):* • *18 years or older*

	• *Haemodynamically significant MB or symptomatic bleeding into a critical area* • *Last dose of FXa inhibitor within 18h of presentation* • *Life expectancy >1 month* *Exclusion criteria:* • *Comfort care only* • *4F-PCC given to reverse FXa prior to surgery for non-haemodynamically significant bleeding* • *Concomitant use of other reversal agents than 4F-PCC*
Intervention	*Institutional guidelines suggested 4F-PCC 50 u/kg for the reversal of oral dFXaI.* *The time of the last dose of oral dFXaI was used to project the dose of andexanet based on the package insert dosing recommendations. Patients who received rivaroxaban > 10 mg (or unknown dose) or apixaban > 5 mg (or unknown dose) within < 8 h of presentation were eligible for high dose andexanet (800 mg bolus followed by 8 mg/min infusion for up to 120 min). All other patients were eligible for low dose of andexanet (400 mg bolus followed by 4 mg/min infusion for up to 120 min).*
Baseline characteristics	*N=46* • *Mean (SD) age: 79 (9)* • *36% female* • *Type of DOAC: 67% apixaban; 36% rivaroxaban* • *41% were on other antithrombotics as well (59% on none)* • *Indication for anticoagulation: NVAF 94%, VTE 4%, NVAF + VTE 2%* • *Indication for coagulopathy reversal: ICH or intraspinal haemorrhage 70%; GI bleed 24%; intrabdominal/intrathoracic bleed 6%* *If patients would have been treated with andexanet alfa, 13% of patients were eligible for high dose and 87% were eligible for low dose*
Primary and secondary endpoints	*Primary outcome: projected cost of andexanet compared to the actual cost of 4F-PCC for the reversal of oral dFXaI-related major bleeding.* *Secondary outcomes: haemostatic efficacy and 30-day thrombotic events in patients who received 4F-PCC for dFXaI-related major bleeding compared to published data of andexanet for dFXaI-related major bleeding*
Method of analysis	*Demographics, 24-h haemostatic efficacy and 30-day thromboembolic event rates were qualitatively compared between the data. Differences between included patients and excluded patients who received 4F-PCC to reverse a dFXaI were evaluated using Chi squared tests for categorical values and Mann–Whitney U non-parametric tests for continuous, non-normally distributed values.*
Subgroup analyses	*Subgroup analyses were made based on bleeding location using the same methods as for the baseline analysis*

Trial name	*RETRACE II*
NCT number	*NCT03093233*
Objective	*Investigate parameters associated with haematoma enlargement in DOAC-related ICH.*
Publications – title, author, journal, year	*Gerner, S.T., et al., Association of prothrombin complex concentrate administration and haematoma enlargement in non-vitamin K antagonist oral anticoagulant-related intracerebral hemorrhage. Ann Neurol, 2018. 83(1): p. 186-196. [5]*
Study type and design	*Retrospective cohort study*
Follow-up time	*3 months*
Population (inclusion and exclusion criteria)	*Inclusion Criteria:* • *DOAC-ICH defined as known to be on treatment with DOAC at ICH-onset* *Exclusion Criteria:* • *ICH related to trauma, tumor, arteriovenous malformation, aneurysmal subarachnoid haemorrhage, acute thrombolysis, or other coagulopathies.*
Intervention	*PCC – median dosage 2000 IU; information on administered weight adapted dosage of prothrombin complex concentrate (PCC) was available in 85 patients (≥25IU/kg: n=57, <25IU/kg: n=28).*

Baseline characteristics	*N=146* • *Type of DOAC: rivaroxaban 75,3% (110); apixaban 14,4% (21); dabigatran 11,2% (15)* • *Overall, 33,5% (49) had haematoma enlargement* • *Descriptive statistics presented for subgroups based on whether patients experienced haematoma enlargement or not* • *70,5% (103) received PCC; 29,5% (43) did not* *Weight adapted dosage of PCC (available in 85 patients): ≥25IU/kg: n=57; <25IU/kg: n=28*
Primary and secondary endpoints	*Primary endpoint: the influence of PCC on haematoma enlargement* *Secondary endpoints: the influence of PCC on mortality and functional outcome*
Method of analysis	*For group comparisons, data were tested for normal distribution by Kolmogorov–Smirnov and Shapiro–Wilk tests. In the case of normal distribution, data were presented as mean (standard deviation) compared using the Student t test, otherwise as median (interquartile range) and compared using the Mann–Whitney U test or Kruskal–Wallis test. For comparison of frequency distribution of categorised variables, Pearson's chi-square test or Fisher's exact test were used. Significance level was set at α=0.05, 2-sided. In a second step, the Bonferroni correction was applied to correct for accumulation of type 1 error in multiple testing. Receiver operating characteristic (ROC) analysis was conducted to investigate the association of anti-Xa levels on admission with haematoma enlargement in patients with factor Xa inhibitor–related ICH. The best cutoff point for discriminating the risk of haematoma enlargement was identified by the Youden index. All multivariate models consisted of a generalised linear model using log-Poisson regression utilizing a robust estimator as covariance matrix to account for bias introduced by skewed distributions and outliers (ie, treatment years and center effects). Secondary outcomes were compared using Pearson's chi-square test and presented as mRS plot at discharge and after 3 months.*
Subgroup analyses	*One subgroup analysis was made by comparing background characteristics among patients with and without haematoma enlargement; however, no outcomes of interest were presented. A second subgroup analysis was made by comparing follow-up imaging based on DOAC; however, no outcomes of interest were presented.* *One outcome of interest, haematoma enlargement, was presented for the subgroup of 103 patients that received PCC for DOAC reversal; however, no additional information was available. Haematoma enlargement was defined as volume increase of >33% compared to initial imaging*

Trial name	*Administration of 4-Factor Prothrombin Complex Concentrate as an Antidote for Intracranial Bleeding in Patients Taking Direct Factor Xa Inhibitors*
NCT number	
Objective	*To evaluate the efficacy and safety of 4F-PCC administration on rivaroxaban- and apixaban-mediated coagulopathy in patients with traumatic and spontaneous ICH*
Publications – title, author, journal, year	*Grandhi, R., et al., Administration of 4-Factor Prothrombin Complex Concentrate as an Antidote for Intracranial Bleeding in Patients Taking Direct Factor Xa Inhibitors. World Neurosurg, 2015. 84(6): p. 1956-61. [15]*
Study type and design	*Retrospective chart review*
Follow-up time	*90 days*
Population (inclusion and exclusion criteria)	*Inclusion criteria:* • *Pre-injury use of apixaban or rivaroxaban* • *Diagnosis of spontaneous ICH or blunt TBI with evidence of ICH on initial non-contrast CT scan* *Exclusion criteria:* • *Received FFP for anticoagulation reversal*
Intervention	*PCC - median dose 3177 IU (2124-4770)*
Baseline characteristics	*N=18* • *Mean age: 79,6* • *54,4% female* • *Mean (SD): GCS score 12,6 (3); ICH score 2,3 (1,3)* • *Type of DOAC: rivaroxaban 89% (16); apixaban 11% (2)* • *Indications for anticoagulation: AF 89%, mAVR 5,6%, lupus anticoagulant 5,6%*

	• *Type of bleed: TBI 44,4%; subarachnoid haemorrhage 5,6%; haemorrhage into metastatic brain lesion 5,6%; haemorrhagic stroke 44,4%*
Primary and secondary endpoints	*Safety outcomes: in-hospital mortality; thromboembolic complications; pulmonary complications* *Efficacy outcomes: ICH progression on repeat head CT or bleeding complication after neurosurgical intervention; 90-day mRS score determined at the follow-up appointment*
Method of analysis	*Patient demographics were presented on an individual level and descriptive statistics presented as means*
Subgroup analyses	

Trial name	*Comparison of outcomes in patients with intracranial hemorrhage on factor Xa inhibitors versus vitamin K antagonists treated with 4-factor prothrombin complex concentrate*
NCT number	
Objective	*Compare outcomes, including mortality rates, of patients with factor Xa inhibitor anticoagulant–associated ICH who were treated with 4F-PCC to those of similar patients with VKA-associated ICH*
Publications – title, author, journal, year	*Harrison, S.K., et al., Comparison of outcomes in patients with intracranial hemorrhage on factor Xa inhibitors versus vitamin K antagonists treated with 4-factor prothrombin complex concentrate. Proc (Bayl Univ Med Cent), 2018. 31(2): p. 153-156. [16]*
Study type and design	*Multicenter chart review study*
Follow-up time	*30 days*
Population (inclusion and exclusion criteria)	*Inclusion criteria:* • *≥18 years old* • *Traumatic or non-traumatic ICH* • *On VKA or DOAC.* *Exclusion criteria:* • *Patients treated with PCC without traumatic/non-traumatic ICH* • *Patients anticoagulated with direct thrombin inhibitors* • *Patients who received fresh frozen plasma as reversal agent*
Intervention	*PCC - recommended dose was 50 U/kg to a maximum of 5000 units for reversal of apixaban and rivaroxaban*
Baseline characteristics	*N=42, whereof 14 were on FXa inhibitors* *Among 14 on FXa inhibitors:* • *Mean age: 74 +/- 8* • *57,2% female* • *Average weight: 79 (+/- 18)* • *Creatinine clearance (mL/min) 65 (+/- 18)* • *14,2% experienced ischemic stroke* • *Indication for anticoagulation: AF 12/14; venous thromboembolic disease 3/14; cerebrovascular accidents 2/14* • *85,7% (12) had spontaneous ICH; 14,2% (2) had trauma ICH* • *Avg haematoma size (mL) was 13,44 (n=12)* • *Avg time from diagnosis to PCC administration: 6h* • *Initial GCS: 13-15 79%; 9-12 14%; 3-8 7%* • *PCC dose: 25 U/kg 14,3% (2); 35 U/kg 14,3% (2); 50 U/kg 71,4% (10)*
Primary and secondary endpoints	*Primary outcome: in-hospital mortality* *Secondary outcomes: post-reversal international normalised ratio; activated partial thromboplastin time; prothrombin time* *Also reported: hospital length of stay (LOS); ICU LOS; neurological function at discharge (disposition); thromboembolic events; haemorrhagic expansion*
Method of analysis	*Presentation characteristics and demographic data were analyzed using frequencies and percentages for categorical variables such as gender, race, and method of arrival; means and standard deviations were used for continuous variables. Where appropriate, tests for differences in population characteristics were performed using chi-square analysis or t tests.*

Subgroup analyses	*The study is presented as a comparison between the two subgroups patients who received PCC for VKA reversal and patients who received PCC for FXa inhibitor reversal*

Trial name	*Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study (the UPRATE study)*
NCT number	
Objective	*To assess the efficacy and safety of 4F-PCCs for the reversal of the anticoagulant effect of rivaroxaban and apixaban in a multicenter, prospective setting*
Publications – title, author, journal, year	*Majeed, A., et al., Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. Blood, 2017. 130(15): p. 1706-1712.[17]*
Study type and design	*Prospective cohort study*
Follow-up time	*30 days*
Population (inclusion and exclusion criteria)	*Inclusion criteria:* • *Patients needing treatment with a PCC for the management of acute and active major bleeding (as defined by ISTH; "active" indicating that there is evidence of blood loss or decreasing haemoglobin or, for ICH, deteriorating neurological symptoms during the past 48≥ hours with radiological evidence of ICH)* • *On rivaroxaban or apixaban* • *Last dose of rivaroxaban or apixaban within 24 hours* *Exclusion criteria:* • *Patients with a do-not-resuscitate order* • *Patients with a drop of haemoglobin without an evident source of bleeding* • *Preoperative reversal of rivaroxaban or apixaban anticoagulation effects* • *Patients with acute coronary syndrome or ischemic stroke within the past 30 days* • *Patients receiving other haemostatic agents prior to administration of PCC*
Intervention	*PCC - 1500 or 2000 IU were given for patients with body weights less or more than 65 kg, respectively. An additional dose of a PCC was allowed at the discretion of the treating physician if the bleeding did not stop after the first PCC dose. This protocol was based on an approximation of a PCC dose equivalent to 25 IU/kg.*
Baseline characteristics	*N=84* • *Median age: 75 years (IQR 70-83)* • *42,9% female* • *Median body weight: 75 kg (IQR 66-80);* • *Type of DOAC: apixaban 46,4%; rivaroxaban 53,6%* • *Indications for anticoagulation: SPAF 75%; VTE 21,4%; SPAF and VTE 3,6%* • *25% had a history of stroke* • *INR: 1,2 (1,1-1,4)* • *APPT: 38 (34-45)* • *Creatinine levels: 77 (62-97)* • *Bleeding locations: ICH 70,2%; GI 15,5%; Visceral 6%; Genitourinary 4,8%; Musculoskeletal 3,5%*
Primary and secondary endpoints	*Effectiveness outcomes: effectiveness of MB management* *Primary safety outcome: objectively verified arterial or venous TE* *Other outcomes presented: change in neurological status; need for surgical intervention; hospital LOS; discharge destinations; 30-day mortality*
Method of analysis	*Continuous variables are presented as medians and interquartile ranges (IQRs) and analyzed with the Mann-Whitney test for skewed distributions. Binomial data are presented as proportions or percentages and were compared by using χ^2 or Fisher's exact test*
Subgroup analyses	*Apixaban, n=39* • *Median age: 77 years (IQR 7-81)* • *43,4% female* • *Median body weight: 75 kg (IQR 67-89);* • *Indications for anticoagulation: SPAF 87,2%; VTE 5,1%; SPAF and VTE 7,7%* • *28,2% had a history of stroke* • *INR: 1,2 (1,1-1,3)* • *APPT: 35 (32-39)* • *Creatinine levels: 77 (61-83)*

	• *Bleeding locations: ICH 74,4%; GI 12,8%; Visceral 5,1%; Genitourinary 5,1%; Musculoskeletal 2,6%* *Rivaroxaban, n=45* • *Median age: 73 years (IQR 68-84)* • *42,2% female* • *Median body weight: 75 kg (IQR 65-80);* • *Indications for anticoagulation: SPAF 64,4%; VTE 2,2%; SPAF and VTE 33,3%* • *22,2% had a history of stroke* • *INR: 1,3 (1,1-1,5)* • *APPT: 41 (36-49)* • *Creatinine levels: 79,5 (63,5-99,5)* • *Bleeding locations: ICH 66,7%; GI 17,8%; Visceral 6,7%; Genitourinary 4,4%; Musculoskeletal 4,4%* *Subgroup analyses were made based on bleeding location and type of DOAC using the same methods as for the baseline analysis*

Trial name	*Application of prothrombin complex concentrate for reversal of direct oral anticoagulants in clinical practice: indications, patient characteristics and clinical outcomes compared to reversal of vitamin K antagonists*
NCT number	
Objective	*Explore patient characteristics, indications and clinical outcomes for reversal of all DOAC patients receiving PCC at a university emergency department in comparison with patients on VKA*
Publications – title, author, journal, year	*Muller, M., et al., Application of prothrombin complex concentrate for reversal of direct oral anticoagulants in clinical practice: indications, patient characteristics and clinical outcomes compared to reversal of vitamin K antagonists. Scand J Trauma Resusc Emerg Med, 2019. 27(1): p. 48. [18]*
Study type and design	*Retrospective cohort study set in the adult emergency department of a hospital in Switzerland*
Follow-up time	*Followed until discharge*
Population (inclusion and exclusion criteria)	*Inclusion criteria:* • *All patients on DOAC or VKA irrespective of the cause* • *Adults (>=18 years)* • *Admitted during the study time* *Exclusion criteria:* • *No documentation of the application of PCC* • *No oral anticoagulation medication documented in medical report* • *Insufficient information to determine anticoagulation status*
Intervention	*PCC median dose 2000 IU (range: 1700-3000) among all DOAC patients (including those not indicated for bleeding)*
Baseline characteristics	*74 were treated for DOAC reversal, 272 for VKA reversal* *Among 74 patients on DOACs::* • *Median age 77 years (IQR 69-82)* • *39,2% female* • *Type of DOAC: rivaroxaban 90,5%; apixaban 6,7%* • *Anticoagulation indications: AF 64,9%; TEs 17,6%; mechanical heart-valve 1,4%; coagulopathy 2,7%; not specified 13,5%* • *A majority had acute life-threatening problems (51,4%) or high urgency (33,8%) triages* • *A majority (93,2%) had "bleeding" as indication* • *Bleeding locations: intracranial 60,8%; GI 18,9%; superficial 5,4%; extremity 2,7%; abdominal 2,7%; thorax 5,4%; eye 1,4%; retroperitoneal 1,4%; haematuria; 1,4%* *No descriptive statistics available for those patients who actually experienced a major bleed*
Primary and secondary endpoints	*In-hospital mortality; procedural outcomes (hospitalization, LOS, need for ICU admission and ICU LOS); need for and amount of blood products given*
Method of analysis	*The study compared patients on DOAC or VKA, which were reversed by PCC. Categorical variables were expressed as absolute numbers, accompanied by relative numbers. Continuous variables were expressed as medians with interquartile ranges. DOAC and VKA patients were compared with respect to the clinical outcomes. Fisher's exact tests were used to compare categorical variables and the Wilcoxon rank sum*

	test to compare continuous variables
Subgroup analyses	

Trial name	*Tolerability and effectiveness of 4-factor prothrombin complex concentrate (4F-PCC) for warfarin and non-warfarin reversals*
NCT number	
Objective	*Evaluate the tolerability and effectiveness of 4F-PCC in a real-world setting.*
Publications – title, author, journal, year	*Santibanez, M., et al., Tolerability and effectiveness of 4-factor prothrombin complex concentrate (4F-PCC) for warfarin and non-warfarin reversals. J Crit Care, 2018. 48: p. 183-190. [19]*
Study type and design	*Retrospective study*
Follow-up time	*14 days*
Population (inclusion and exclusion criteria)	*Inclusion criteria:* • *Adults (≥18 years)* • *Received at least one dose of 4F-PCC* *Exclusion criteria:* • *Given 4F-PCC at an outside hospital* • *Patients diagnosed with coagulopathy who were reversed for documented or suspected coagulopathy while neither actively bleeding nor undergoing emergent surgery*
Intervention	*PCC - 88,1% of DOAC patients received 25 U/kg. Actual PCC dose units/kg 25,8 (range: 23,1-27,3)*
Baseline characteristics	*Descriptive statistics for 165 patients treated for MB (36 of these were on DOACs):* • *Age 74 (65-81)* • *44,8% female* • *Avg weight 74,5 kg (range: 64,3-89,4)* • *Type of bleed: ICH 64,2% (whereof 38,7% intraparenchymal haemorrhage, 34,9% subdural haematoma, 18,9% subarachnoid haemorrhage, 5,7% intraventricular haemorrhage, 1,9% epidural haemorrhage); Other 14,5%; GI 13,3%; diffuse intraoperative bleeding 7,9%* • *Type of DOAC: Rivaroxaban 52,8%; apixaban 36,1%: dabigatran 11,1%* • *Indication for anticoagulation: AF 59,4%; VTE prophylaxis or treatment 14,5%; prosthetic valve 7,3%; LVAD 3%, cerebrovascular accident 6,1%; other 4,8%, antiphospholipid syndrome 1,8%; chronic thromboembolic pulmonary hypertension 0,6%; post-MI 0,6%* • *Thromboembolic history: cerebrovascular accident 23,6%; MI 10,9%; upper and lower extremity DVT 12,1%; other 7,9%; PE 7,9%*
Primary and secondary endpoints	*Primary outcome: TEs within 14 days including upper and lower extremity DVT, PE, ischemic stroke, MI, line-associated thrombosis, and any other documented thrombosis* *Secondary outcome: haemostatic effectiveness within 24 h*
Method of analysis	*Descriptive statistics were used to assess for significant risk factors for thromboembolic events and haemostatic effectiveness. Categorical variables were evaluated with the $\chi 2$ or Fisher's exact test. Continuous variables were evaluated with the independent t-test. A univariable analysis comparing patients who experienced thromboembolic events with those who did not was conducted using established thrombotic risk factors. All variables with $p \leq 0.2$ in the univariable analysis were included in a multivariable analysis to determine independent factors associated with thromboembolic events*
Subgroup analyses	*Haemostatic effectiveness was evaluable in 32/36 patients treated for DOAC-related MBs*

Trial name	*Four-factor prothrombin complex concentrate improves thrombin generation and prothrombin time in patients with bleeding complications related to rivaroxaban: a single-center pilot trial*

NCT number	
Objective	*The aim of this study was to test the efficacy of reversing the DOAC rivaroxaban using four-factor PCC (prothrombin complex concentrate), a non-specific reversing agent.*
Publications – title, author, journal, year	*Schenk, B., et al., Four-factor prothrombin complex concentrate improves thrombin generation and prothrombin time in patients with bleeding complications related to rivaroxaban: a single-center pilot trial. Thromb J, 2018. 16: p. 1. [20]*
Study type and design	*"The present study is a single-centre, analytic, observational, prospective, open-labelled, single-armed, non-commercial clinical pilot trial."*
Follow-up time	*30 days*
Population (inclusion and exclusion criteria)	*Inclusion criteria:* • *≥18 years of age* • *Receiving rivaroxaban* • *Acute need of reversal of rivaroxaban or life-threatening bleeding* *Exclusion criteria:* • *Patients already receiving pro-coagulant therapies* • *A greater risk for thromboembolic events than for bleeding* • *Pregnancy* • *Suspected or confirmed sepsis* • *Recent history of thromboembolic events* • *Active participation in another clinical trial* • *Refusal to participate*
Intervention	*PCC 25 U/kg*
Baseline characteristics	*14 patients (1 was later excluded)* • *Median age 80 years (range: 47-96)* • *Median weight 76 kg (range: 52-99)* • *Median height 170 cm (range: 156-183)* • *Underlying diseases: ICH (6/13); subdural haematoma (4/13); haemorrhage (2/13); GI bleed (1/13)* • *2/13 patients had received additional antiplatelet medication* • *Concomitant medication (from V1 to V7), with potential influence on coagulation: anticoagulant medication (12/13); catecholamines (10/13); antibiotics (6/13); procoagulant medication (1/13); anti-fibrinolytics (1/13) and blood products (1/13);* • *10 received noradrenaline, 7 enoxaparin, 2 rivaroxaban, 1 danaparoid, fibrinogen concentrate, tranexamic acid and erythrocyte concentrate*
Primary and secondary endpoints	*Primary outcome: coagulation status after administration of PCC* *Secondary outcomes: development of the following parameters from V1 to V10 and their correlation with measured rivaroxaban levels: thrombin generation, single factor profiles, standard coagulation tests PT, aPTT, fibrinogen, AT, and thromboelastometry (ROTEM®)*
Method of analysis	*A descriptive analysis of all measured blood characteristics was performed. The Wilcoxon signed-rank test was used to evaluate the primary endpoint and all other differences in coagulation measurements between baseline and samples from the same patient at V2 to V10. To evaluate correlations between rivaroxaban level and blood coagulation assays and coagulation factor activities Pearson's correlation was used.*
Subgroup analyses	

Trial name	*Prothrombin Complex Concentrate for Major Bleeding on Factor Xa Inhibitors: A Prospective Cohort Study*
NCT number	
Objective	*To evaluate the use of PCC at a dose of 2,000 units for the management of factor Xa-inhibitor–associated major bleeds.*
Publications – title, author, journal, year	*Schulman, S., et al., Prothrombin Complex Concentrate for Major Bleeding on Factor Xa Inhibitors: A Prospective Cohort Study. Thromb Haemost, 2018. 118(5): p. 842-851. [21]*

Study type and design	*Prospective observational multicentre cohort study performed at hospitals in Canada, where PCC is available through the Transfusion Medicine Departments and where a hospital protocol suggests or recommends the use of this concentrate at a standardised dose of 2,000 units for reversal of factor Xa-inhibitor–associated bleeding.*
Follow-up time	*30 days*
Population (inclusion and exclusion criteria)	*Inclusion criteria:* • *Received infusion with PCC (2000 IU) for MB (ISTH definition) while on rivaroxaban or apixaban* • *Had not received other haemostatic agents prior to administration of PCC* • *Written informed consent* *Exclusion criteria:* • *"Do not resuscitate" orders given before treatment with PCC due to severity of bleed* • *Drop of haemoglobin without evidence of a source of bleeding* • *Acute coronary syndrome or ischemic stroke during the past 30 days*
Intervention	*PCC 2000 IU; mean dose IU/kg was 26,4 (SD 7,7)*
Baseline characteristics	*N=66* • *Age (SD) 76,9 (10,4)* • *33% female* • *Median weight (IQR) 81 (68-90)* • *Type of DOAC: rivaroxaban 56%; apixaban 44%* • *Indication for anticoagulation: AF 82%; VT 13%; AF + VT 3%; ischemic stroke 2%* • *Type of bleeding: ICH 55%; intraspinal 3%; GI 24%; retroperitoneal 5%; intramuscular 3%; other 11%*
Primary and secondary endpoints	*Primary outcome: Proportion of patients with good effectiveness of PCC as assessed by the emergency physician or most responsible physician* *Secondary outcome: other blood products used; decrease in haemoglobin from the first reported level on admission to the lowest level after application of PCC; ICU LOS; hospital LOS* *Primary safety outcome: TEs (symptomatic DVT or PE, ischemic stroke, heart valve or cardiac chamber thrombosis, symptomatic peripheral arterial thrombosis or MI)* *Secondary safety outcomes: 30-day TEs; mortality*
Method of analysis	*Results are reported as means (± standard deviation [SD]) or, in case of skewed distribution, as median and interquartile range (IQR) as appropriate. Comparisons between groups were performed with Mann–Whitney U-test.*
Subgroup analyses	*Subgroup analyses were made based on type of bleed using the same methods as the baseline analysis. Furthermore, several post-hoc analyses were made on the proportion of patients reaching good haemostasis based on other criteria (such as the ISTH criteria and those criteria used in ANNEXA-4 for comparability)*

Trial name	*Treatment of apixaban- and rivaroxaban-associated major bleeding using 4-factor prothrombin complex concentrate*
NCT number	
Objective	*To assess the achievement of effective clinical hemostasis in DOAC-treated patients with the use of 4F-PCC*
Publications – title, author, journal, year	*Sheikh-Taha, M., Treatment of apixaban- and rivaroxaban-associated major bleeding using 4-factor prothrombin complex concentrate. Intern Emerg Med, 2019. 14(2): p. 265-269. [22]*
Study type and design	*Retrospective chart review*
Follow-up time	*Patients were followed until hospital discharge or death*
Population (inclusion and exclusion criteria)	*Inclusion criteria:* • *MB (ISTH definition)* • *Received apixaban or rivaroxaban* • *Received 4F-PCC* *Exclusion criteria:* • *Given 4F-PCC for emergency surgery or procedure*

Intervention	*PCC – 50 U/kg*
Baseline characteristics	*N=29* • *Mean (SD) age 73,8 (12)* • *55,2% female* • *Indication for DOAC: AF 79,3%; DVT/PE 17,2%; hip replacement 3,4%* • *DOAC: rivaroxaban 55,2%, apixaban 44.8%* • *Bleeding site: ICH 72,4%; GI 13,8%; Nose 6,9%; Genitourinary 3,4%; musculoskeletal 3,4%* • *Baseline coagulation tests: INR 1,5 (1-2,9); aPPT 36,1 (27-63)* • *Mean (SD) comorbidities: 5,2 (1,4)* • *Mean (SD) concomitant drugs used: 9,2 (4)* • *Mean hospital LOS: 5,9 (range: 2-15)*
Primary and secondary endpoints	*Not presented*
Method of analysis	*Data were analyzed with descriptive statistics and frequency distributions.*
Subgroup analyses	*Subgroup analyses were made based on bleeding site and type of DOAC, using the same method as in the baseline analysis* *Descriptive statistics by type of DOAC was only available for baseline coagulation tests:* • *Apixaban patients, mean (range): INR 1,4 (1-2,4); aPTT 35,7 (26,3-62,8)* • *Rivaroxaban patients, mean (range): INR 1,7 (1,1-2,9); aPTT 37,4 (26,7-63,4)*

Trial name	*Four-factor prothrombin complex concentrate for life-threatening bleeds or emergent surgery: A retrospective evaluation*
NCT number	
Objective	*To evaluate the safety and effectiveness of 4F-PCC in a real-world setting based on an institutional protocol that does not have strict exclusion criteria.*
Publications – title, author, journal, year	*Sin, J.H., K. Berger, and C.A. Lesch, Four-factor prothrombin complex concentrate for life-threatening bleeds or emergent surgery: A retrospective evaluation. J Crit Care, 2016. 36: p. 166-172. [23]*
Study type and design	*Retrospective chart review*
Follow-up time	*14 days/hospital discharge/death*
Population (inclusion and exclusion criteria)	*Inclusion criteria:* • *≥18 years* • *Received at least one dose of 4F-PCC* *Exclusion criteria:* • *None*
Intervention	*Recommended dose for DOAC reversal was 25 IU/kg with a maximum of 2500 IU*
Baseline characteristics	*63/93 were treated for bleeding, among these 63:* • *Mean age was 68 (range: 59-81)* • *38,1% female* • *Mean weight was 78,6 kg (67,1-100,4)* • *Type of DOAC: rivaroxaban 9,5%; apixaban 4,8%; dabigatran 3,2%* • *Type of bleed: ICH 66,7%; GI 11,1%; other haemorrhage 22,2%* • *Reason for anticoagulation: AF 63,6%; ventricular assist device 3,6%; prosthetic valve 12,7%; DVT treatment 7,3%; PE treatment 1,8%; antiphospholipid syndrome 3,6%; CTEPH 1,8%; post-MI 1,8%; other 12,7%* • *Past medical history: hypertension 65,1%; AF 55,6%; hyperlipidemia 50,8%; coronary artery disease 39,7%; heart failure 20,6%; diabetes 27%; chronic kidney disease 14,3%; coronary artery bypass graft 14,3%; stent placement 9,3%; peripheral vascular disease 7,9%: COPD 6,3%* • *Thromboembolic history (n=26): MI 15,4%; ischemic stroke 50%; lower extremity DVT 19,2%, PE 11,5%; upper extremity DVT 7,7%; other 23,1%*

Primary and secondary endpoints	*Primary safety outcome: TE within 14 days* *Secondary outcomes: haemostatic effectiveness (within 24 h; among patients treated for bleeds); INR correction and INR rebound (among patients on warfarin)*
Method of analysis	*Descriptive statistics were utilised and compared with the chi-squared test or the Fisher's exact test as appropriate*
Subgroup analyses	*Subgroup analyses were made based on type of DOAC*

Trial name	*Safety, efficacy, and cost of four-factor prothrombin complex concentrate (4F-PCC) in patients with factor Xa inhibitor-related bleeding: a retrospective study*
NCT number	
Objective	*To assess the safety and efficacy of 4F-PCC for the management of major bleeding related to oral fXa inhibitors*
Publications – title, author, journal, year	*Smith, M.N., et al., Safety, efficacy, and cost of four-factor prothrombin complex concentrate (4F-PCC) in patients with factor Xa inhibitor-related bleeding: a retrospective study. J Thromb Thrombolysis, 2019. 48(2): p. 250-255. [24]*
Study type and design	*Retrospective study*
Follow-up time	*Until hospital discharge*
Population (inclusion and exclusion criteria)	*Inclusion criteria:* • *≥18 years* • *Received 4F-PCC for major bleeding associated with FXa inhibitor* *Exclusion criteria:* • *Pregnancy* • *Incarceration* • *Perioperative reversal unrelated to bleeding* • *In order to limit bias toward worse outcomes* • *Patients with an intracranial haemorrhage (ICH) and initial Glasgow Coma Scale (GCS) less <7* • *Patients with acute coronary syndrome or ischemic stroke within 30 days prior to reversal*
Intervention	*PCC – 25-50 U/kg up to 5000 units*
Baseline characteristics	*N=31* • *Median (IQR) age was 74 (69-84)* • *Median (IQR) weight 85 (68-102)* • *26,8% female* • *Type of DOAC: apixaban 54,8%; rivaroxaban 45,2%* • *Indication for anticoagulation: AF 90,3%; VT 9,7%* • *Type of bleed: ICH 58,1% (among which 38,9% intracerebral, 38,9% subdural, 22,2% subarachnoid); pericardial 16,1%; musculoskeletal 12,9%; intraspinal 3,2%; intrathoracic 3,2%; GI 3,2%; epistaxis 3,2%*
Primary and secondary endpoints	*Primary outcome: effectiveness of 4F-PCC for treating FXa inhibitor-related MBs* *Secondary outcomes: TE rates during hospitalization; cost analysis comparing 4F-PCC with andexanet alfa for reversal of oral FXa inhibitors*
Method of analysis	*Data was evaluated using descriptive statistics. Normally distributed data was described with means [standard deviation (SD)] and medians [interquartile range (IQR)] were used to describe nonparametric and non-normally distributed data. As a pilot study with no comparator group, there was no calculated sample size and all eligible patients during the study period were included.*
Subgroup analyses	

Trial name	*Safety of 4-factor prothrombin complex concentrate (4F-PCC) for emergent reversal of factor Xa inhibitors*

NCT number	
Objective	*Study the safety of 4F-PCC for emergent reversal of FXa inhibitors*
Publications – title, author, journal, year	*Tao, J., E.N. Bukanova, and S. Akhtar, Safety of 4-factor prothrombin complex concentrate (4F-PCC) for emergent reversal of factor Xa inhibitors. J Intensive Care, 2018. 6: p. 34. [26]*
Study type and design	*Single-center retrospective review of medical records*
Follow-up time	*14 days*
Population (inclusion and exclusion criteria)	*Inclusion criteria:* • *Have received 4F-PCC for reversal of rivaroxaban, apixaban or edoxaban for emergency surgery, invasive procedures or during episodes of major bleeding* *Exclusion criteria:* • *Received 4F-PCC for other purposes than reversing FXa inhibitors* • *Under 18 years of age*
Intervention	*PCC – mainly 25-50 U/kg (1 patient received >50 U/kg)*
Baseline characteristics	*N=43* • *Median age was 74* • *46,5% female* • *Type of DOAC: rivaroxaban 48,8%; apixaban 51,2%* • *Indication for anticoagulation: AF 69,8%; DVT/PE 20,9%; AF and DVT/PE 7%; lower extremity venous bypass graft 2,3%* • *Indication for reversal of FXa: GI 39,5%; ICH (non-traumatic) 20,9%; ICH (traumatic) 16,3%; trauma 14%; other 11,6%* • *Invasive procedure after 4F-PCC (69,8%): GI endoscopy 37,2%; interventional radiology embolization/coiling 7%; craniotomy 7%; orthopedic 7%; other 11,6%*
Primary and secondary endpoints	*Outcomes reported: timing and type of DVT prophylaxis after 4F-PCC administration; TEs within 14 days*
Method of analysis	*To ensure fidelity of data abstraction, all the included charts were analyzed by two reviewers, with inter-observer agreement found to be congruent on all data fields. Data was analyzed using point and interval estimation to approximate the rate and confidence interval of thromboembolic events in the general population. A breakdown of TEs was reported in a descriptive fashion.*
Subgroup analyses	*Subgroup analyses were conducted based on type of DOAC and type of bleeding using the same methodology as the baseline analysis*

Trial name	*Clinical experience reversing factor Xa inhibitors with four-factor prothrombin complex concentrate in a community hospital*
NCT number	
Objective	*To characterise the current use of 4F-PCC and determine adherence to institutional recommendations.*
Publications – title, author, journal, year	*Tellor, K.B., N.S. Barasch, and B.M. Lee, Clinical experience reversing factor Xa inhibitors with four-factor prothrombin complex concentrate in a community hospital. Blood Transfus, 2018. 16(4): p. 382-386. [27]*
Study type and design	*Retrospective study of all patients who received 4F-PCC for reversal of a FXa inhibitor were included in the evaluation. Patients requiring reversal due to warfarin or dabigatran therapy were not included. An electronic medical record was used to collect each patient's data.*
Follow-up time	*Not reported; one TE was reported after 15 days*
Population (inclusion and exclusion criteria)	*Inclusion criteria:* • *Patients who received 4F-PCC for reversal of a FXa inhibitor*

Intervention	*PCC – recommended dose was 50 U/kg*
Baseline characteristics	*N=29* • *Avg age 72,7* • *48,3% female* • *Avg LOS: 5,3 days* • *Concomitant antiplatelet 41,4%* • *Type of DOAC: apixaban 37,9%; rivaroxaban 62,1%* • *Indication for anticoagulation: AF 69%; "other" 6,9%; bioprosthetic valve 3,4%; VT 24,1%* • *89,7% had a major bleed according to ISTH criteria, 3,4% had clinically relevant non-major bleed, criteria were not applicable for 6,9%* • *Indication for 4F-PCC: emergent surgery 10,3%; GI bleed 58,6%; ICH 20,7%; intraperitoneal bleed 2,7%; non-critical site 3,4%; retroperitoneal bleed 3,4%*
Primary and secondary endpoints	*Not reported but seemingly discharge disposition, in-hospital mortality and TEs*
Method of analysis	*Descriptive statistics reporting number and percentage of patients*
Subgroup analyses	*Subgroup analyses were conducted based on type of DOAC and type of bleeding using the same methodology as the baseline analysis*

Trial name	*Management of major bleeding and outcomes in patients treated with direct oral anticoagulants: results from the START-Event registry*
NCT number	
Objective	*To describe the actual management of bleeding or recurrent thrombotic events in routine clinical practice.*
Publications – title, author, journal, year	*Testa, S., et al., Management of major bleeding and outcomes in patients treated with direct oral anticoagulants: results from the START-Event registry. Intern Emerg Med, 2018. 13(7): p. 1051-1058. [28]*
Study type and design	*Prospective, observational, multicenter, international registry study*
Follow-up time	*6 months; outcomes also reported at hospital discharge*
Population (inclusion and exclusion criteria)	*Inclusion criteria:* • *Patients ≥18 years of age presenting with a major bleed (ISTH definition)*
Intervention	*PCC, unknown dosage*
Baseline characteristics	*N=117* • *23% (27 patients) were treated with PCC* • *Median age: 79 years (IQR: 74,85)* • *38% female* • *Type of DOAC: rivaroxaban 43,6%; apixaban 27,3% ; dabigatran 27,3%; 1,7% edoxaban* • *Indication for anticoagulation: NVAF 84%, VTE 16%* • *8,5% had a history of bleeding* • *Major bleeding: spontaneous 80,3%* • *Type of bleed: ICH 45,3%: GI 35,9%; muscular haematoma 6,1%; retroperitoneal 3,4%; haematuria 2,5%; retinal 1,7%; pericardial 1,7%; metrorrhagia 0,9%; other 2,5%*
Primary and secondary endpoints	*Mortality; disability as measured on the Barthel index*
Method of analysis	*Descriptive analysis was performed. Continuous variables are expressed as median and interquartile (IQR) or as median and range. Categorical variables are expressed as frequencies and percentages.*
Subgroup analyses	*Subgroup analyses were conducted based on indication for anticoagulation, type of DOAC and location of bleeding using the same methodology as the baseline analysis*

7.3 Guideline recommendations for reversal of apixaban and rivaroxaban

Guideline	Recommendation	Publication year
ACC [70]	Consider: activated charcoal for all patients 1st line: if available, andexanet alfa 2nd line: if andexanet is not available, administer 4F-PCC or aPCC	2019 (app update)
AC Forum [38]	Suggested: andexanet alfa If andexanet alfa is not available: 4F-PCC	2019
ACCP [39]	Management framework: NOAC-specific reversal agent If NOAC-specific agent is not available: PCC	2018
ACEP [33]	Recommended: andexanet alfa Alternative: PCC	2019
AHA/ACC/HRS [36]	Can be useful: andexanet alfa	2019
ASH [35]	Suggested: andexanet alfa or 4F-PCC	2018
BSG [40]	Recommended: andexanet alfa	2019
EHRA [42]	Recommended: andexanet alfa Alternative: 4F-PCC, aPCC	2018
ESO [37]	1st line: andexanet alfa 2nd line: 4F-PCC	2019
NCCN [43]	Consider: activated charcoal. Recommended: andexanet alfa Alternatives: aPCC, 4F-PCC, rFVIIa, 3F-PCC	2019
Trauma task force [41]	Suggested: TXA or PCC can be considered until specific antidotes are available	2019

Anticoagulation (AC) Forum Guidance: Reversal of Direct Oral Anticoagulants
In patients with rivaroxaban-associated or apixaban associated major bleeding in whom a reversal agent is warranted, we suggest treatment with andexanet alfa dosed according to the US FDA label.[38]

American College of Chest Physicians (ACCP): CHEST Guideline – Antithrombotic Therapy for Atrial Fibrillation
In a patient with serious bleeding, a specific reversal agent (where available) should be used instead. General haemostatic agents as nonspecific agents are less effective in reversing coagulation abnormalities and have not been shown to improve outcomes, and are potentially prothrombotic.[39]

Anticoagulant Reversal Strategies in the Emergency Department Settings: Recommendations of a Multidisciplinary Expert Panel (ACEP)
Therefore, we suggest prothrombin complex concentrate for direct oral anticoagulant treatment only if first line reversal agents (e.g. idarucizumab, andexanet alfa) are unavailable.[33]

AHA/ACC/HRS: Focused Update of the 2014 Guideline for the Management of Patients With Atrial Fibrillation
Andexanet alfa can be useful for the reversal of rivaroxaban and apixaban in the event of life-threatening or uncontrolled bleeding.[36]

American Society of Hematology (ASH): Guidelines for Management of Venous Thromboembolism
For patients with life-threatening bleeding during oral direct Xa inhibitor treatment of VTE, the ASH guideline panel suggests using coagulation factor Xa (recombinant), inactivated-zhzo, in addition to cessation of oral direct Xa inhibitor rather than no coagulation factor Xa (recombinant), inactivated-zhzo

(conditional recommendation based on very low certainty in the evidence about effects⊕). Remark: This recommendation does not apply to non-life-threatening bleeding. No data are available comparing the efficacy of 4-factor PCC and coagulation factor Xa (recombinant), inactivated-zhzo. The guideline panel offers no recommendation for 1 approach over the other.[35]

BSG: UK national guideline on acute lower gastrointestinal bleeding
We recommend considering treatment with inhibitors such as idarucizumab or andexanet for life-threatening haemorrhage on direct oral anticoagulants.[40]

EHRA: Practical Guide on the Use of NOACs in Patients With Atrial Fibrillation
Based on the ongoing ANNEXA-4 study (which, in contrast to REVERSE-AD only includes patients with major/life-threatening bleeding), andexanet alpha may become the first choice of therapy in life-threatening bleeding under FXa-inhibitor therapy (pending its regulatory approval and availability).[42]

European Stroke Organisation – Reversal of Oral Anticoagulants in Acute Stroke
We recommend using andexanet alfa if available – in adult patients with ICH occurring during use of rivaroxaban or apixaban.[37]

NCCN: Cancer-Associated Venous Thromboembolic Disease Guidelines
Beneficial effects have been ascribed to the following:

- Consider oral charcoal if dose within 2 hours of ingestion and repeat within 6 hours
- Administer:
  - Andexanet alfa (consider for patient with intracranial hemorrhage)
  - Alternative options may include: · aPCC
    · 4-factor PCC
    · rhFVIIa

If 4-factor PCC is unavailable or patient is allergic to heparin and/or a history of HIT in the last 12 months then administer 3-factor PCC.[43]

Task Force for Advanced Bleeding Care in Trauma: The European Guideline on Management of Major Bleeding and Coagulopathy Following Trauma
If bleeding is life-threatening, we suggest administration of TXA 15 mg/kg (or 1 g) intravenously and that the use of PCC (25–50 U/kg) be considered until specific antidotes are available. (Grade 2C).[41]

7.4 Rosenbaum sensitivity analysis

The Rosenbaum sensitivity analysis tests how robust results are to confounding caused by unobserved variables affecting both treatment assignment and outcome ('confounding variables'), using a parameter called gamma (Γ).[15] Let $\pi_{i=j,k}$ represent the probability of receiving the treatment of interest (in the case of this analysis, andexanet alfa) for individual i, conditional on a vector of relevant variables for each individual, i, $x_{i=j,k}$. The Γ parameter defines bounds within which the ratio of the odds of receiving treatment for a treated individual, j, and control individual, k, who have identical covariate observations $x_j = x_k$, is hypothesised to sit.

EQUATION 1. THE HYPOTHESIS TESTED IN THE ROSENBAUM SENSITIVITY ANALYSIS FOR A RANGE OF Γ

$$\frac{1}{\Gamma} \leq \frac{\frac{\pi_j}{1-\pi_j}}{\frac{\pi_k}{1-\pi_k}} \leq \Gamma$$

When we generate results and interpret their p values relative to a given significance level without conducting any sensitivity analysis, we assume that the condition set out in Equation 1 need only hold for $\Gamma = 1$. That is to say that we assume that there are no confounding variables so $\pi_j = \pi_k | x_j = x_k$.

In the Rosenbaum sensitivity analysis, a range of different hypotheses are tested, each of which postulates that the condition in Equation 1 holds for a different value of Γ > 1, beginning with 2 ≥ Γ ≥ 1.[15] We thereby test by what factor confounding variables would have to cause $\frac{\pi_j}{1-\pi_j}$ to differ from $\frac{\pi_k}{1-\pi_k}$ for our statistical inference to change. The results of the test indicate whether the statistical significance of our base case results would change if the assumptions we could make around the impact of unobserved covariates became incrementally weaker, given a certain significance level. Here, the significance level α used was 0.05.

For example, if we hypothesise that the condition in Equation 1 holds for Γ = 1.8 and we get a p value of 0.03 when testing this, we can assume that the condition holds true. That is to say that if unobserved variables caused $\frac{\pi_j}{1-\pi_j}$ to differ from $\frac{\pi_k}{1-\pi_k}$ by no more than a factor of 1.8 and no less than a factor of 1/1.8 = ~0.56, then our inference around the statistical significance of our base case results would not change.

The Rosenbaum sensitivity analysis was conducted in R Studio software, using the *rbounds* package and approach described by Keele 2010. [15] The *binarysens* command was used to generate p values associated with values of 2 ≥ Γ ≥ 1 for a propensity score matching analysis with a binary outcome, as recommended by Keele 2010. [15] Data outputs from the *match* command in the *MatchIt* package were manipulated into a list format, in order to be appropriate inputs for the *binarysens* command.

7.5 Other considerations specified in the protocol

7.5.1 Statement regarding the possible prothrombotic effect of andexanet alfa

The thrombotic concern for Andexanet can be accounted for through appropriate pharmacological characterisation of the molecule, its interaction with relevant proteins of the coagulation cascade and also the clinical findings resultant from proactively monitoring for thrombosis as part of ANNEXA clinical study safety oversight.

Pharmacology of Andexanet Alfa

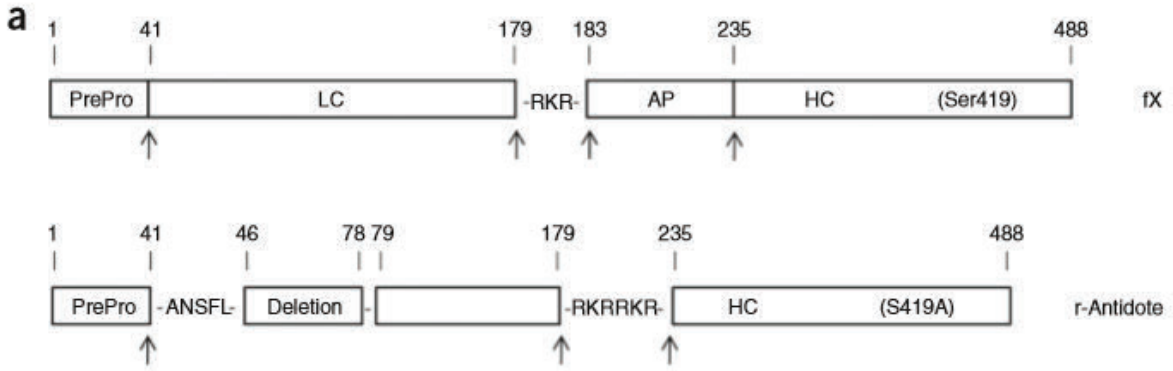
Andexanet is a modified version of native FXa, resulting in a protein that can bind to FXa inhibitors and counteract their activity but is no longer capable of assembly into the prothrombinase complex. It is expressed in Chinese hamster ovary (CHO) cells and purified from conditioned medium.

The three specific modifications included:

1) Deletion of a 34-residue fragment (residues 46–78) that contains the 11 GLA residues

2) Replacement of the activation peptide (AP) with ArgLysArg (RKR) to form the RKRRKR linker that connects the light chain (LC) to the heavy chain (HC)
3) Mutation of the active-site serine to alanine (S419A).

FIGURE A 1. SCHEMATIC ILLUSTRATION OF THE DOMAIN STRUCTURE OF FULL-LENGTH HUMAN FX AND ANDEXANET ALFA (PRT064445).



The pharmacological activity of andexanet has been characterised and subsequently found through thrombin generation assay to have a reduced capacity to generate thrombin due to reduced capacity to incorporate into the prothrombinase complex due to lack of GLA domain in contrast to full length FXa. [71]

Andexanet has been characterised to interact with tissue factor pathway inhibitor with an affinity similar to native FXa (KiXa-TFPI=0.03nM, KdAnXa-TFPI=0.07nM).

One of the primary physiologic functions of TFPI is to down-regulate the activity of the FVIIa/TF complex. Therefore, the effect of the andexanet-TFPI interaction on FVIIa/TF activity was also determined. Unlike FXa-TFPI, however, the Andexanet-TFPI complex does not inhibit FVIIa/TF enzymatic cleavage of a fluorogenic substrate or FX activation - a finding likely due to Andexanet's lack of the Gla-domain.

Andexanet binds to FXa inhibitors, including rivaroxaban with high affinity (Kd=0.5-1.5nM). Andexanet binds to TFPI as evidenced by its partial blockade by a TFPI-K2 antibody.

Furthermore, andexanet binding was almost completely blocked by rivaroxaban, indicating that co-administration with a FXa inhibitor could dampen the andexanet-TFPI interaction. Andexanet alone has minimal effect on thrombin generation parameters including ETP or peak thrombin, while rivaroxaban alone reduces both parameters dose-dependently with increasing rivaroxaban anti-FXa activity. With andexanet + rivaroxaban, however, the andexanet-TFPI interaction leads to enhanced thrombin generation at similar rivaroxaban anti-FXa levels. Competitive interaction of andexanet with TFPI and FXa inhibitors could enhance thrombin generation and reversal of anticoagulation in bleeding patients at clinically relevant andexanet doses/regimens for FXa inhibitors.[72]

Pre-clinical characterisation of Andexanet-TFPI interaction

The PK of andexanet was evaluated in single and multiple dose studies in male rats and monkeys (both rhesus and cynomolgus). In one study rats were administered a series of successive doses of andexanet after oral administration of rivaroxaban. The objective of combination studies was to determine the effect of andexanet on the PK of rivaroxaban and the effect of rivaroxaban on andexanet PK.[73]

When administered as intended, in the presence of the FXa inhibitor rivaroxaban, andexanet PK becomes more complex. A 1 mg/kg dose of andexanet appeared to be affected by rivaroxaban and have higher plasma concentrations and exposure than in the absence of rivaroxaban. However, this effect largely disappeared at the 5 mg/kg dose of andexanet and it was postulated that this effect may be due to an interaction with tissue factor pathway inhibitor (TFPI) on the surface of endothelial cells that can sequester a portion of andexanet. Rivaroxaban and other FXa inhibitors may disrupt or decrease this interaction, restoring the sequestered andexanet to the circulating plasma concentration.

Clinical Findings

ANNEXA-A and ANNEXA-R were both phase III registration enabling studies for andexanet. Healthy older volunteers were given 5 mg of apixaban twice daily or 20 mg of rivaroxaban daily. For each factor Xa inhibitor, a two-part randomised placebo controlled study was conducted to evaluate andexanet administered as a bolus or as a bolus plus a 2-hour infusion. The primary outcome was the mean percent change in anti–factor Xa activity, which is a measure of factor Xa inhibition by the anticoagulant.

In addition to the demonstrable reduction in anti-Xa activities post andexanet administration for subjects administered apixaban or rivaroxaban, there was a demonstrable elevation of prothrombotic markers. d-Dimer and prothrombin fragments 1 and 2 were measured in all participants, and transient elevations were noted that generally returned to the normal range within 24 to 72 hours. Despite this no clinical thrombotic adverse events were observed in healthy elderly subjects. [74]

ANNEXA-4 is a Phase IIIb/IV multicenter, prospective, open-label, single-group study. Patients were enrolled at 63 centers in North America and Europe.[12]

TFPI is an endogenous inhibitor of FXa and circulates in blood as full-length (free) and truncated forms. Just like binding to other FXa inhibitors, administration of andexanet was expected to decrease the TFPI levels due to andexanet-TFPI interaction. The effect was assessed by measuring the free (the most active form) and total TFPI antigen levels, as well as the TFPI activity.

For patients enrolled under protocol amendment 4, TFPI was collected at baseline (i.e., prior to andexanet treatment), end of infusion (EOI), 4, 8, 12, 24, 48, and 72 hours, and 7 days post andexanet treatment. Tissue Factor Pathway Inhibitor Activity, Free TFPI antigen, and Total TFPI antigen were determined. Change from baseline for each time point was calculated. TFPI determination was performed from samples sent to central laboratory. Analysis of TFPI was an exploratory endpoint.

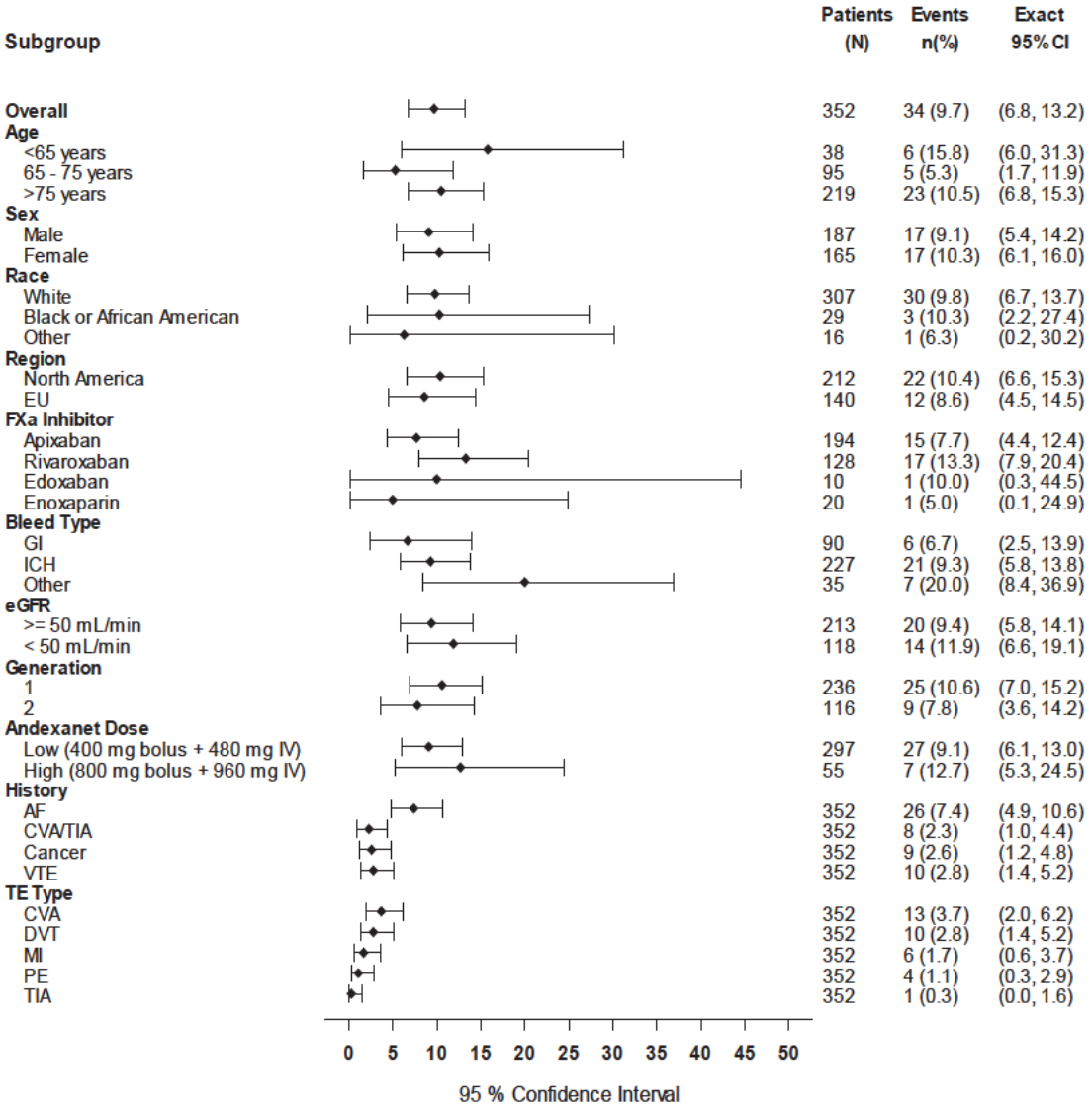
For TFPI activity, the median baseline level was 1.3 U/mL (95% CI 1.2-1.5), which was decreased to 0.6 U/mL (95% CI 0.5-0.6) at EOI and returned to the baseline level on Day 3 post infusion (1.2 U/mL [95% CI 1.1-1.4]). For free TFPI, the median baseline level was 30.9 ng/mL (95% CI 28.4-33.7) which decreased to 5.3 ng/mL (95% CI 4.8-5.9) at EOI. This level increased over time, reaching baseline levels by Day 3 post infusion (30.4 ng/mL [95% CI 27.8-34.4]). The time course and change in total TFPI was of similar magnitude (median baseline 120.6 ng/mL [95% CI 111.7-132.9], EOI 39.9 ng/mL [95% CI 38.0-44.2], and Day 3 post infusion 121.1 [95% CI 111.4-133.6]).

Thrombotic events were pre-specified as adverse events of special interest within the protocol and subject to proactive safety monitoring. Additionally, an external adjudication committee (EAC) operating through charter reviewed all investigator reported thrombotic events according to pre-specified diagnostic criteria. The committee reviewed all clinical details including review of source documents with the capability to raise queries through sponsor as part of ongoing data review/cleaning.

The Safety Population (N=352) consists of all patients who received any amount of andexanet across the low and high dose regimens. All 352 patients in the Safety Population received at least a partial dose of andexanet. Within the Safety Population, 297 patients (84.4%) received the low dose regimen of andexanet (i.e., 400 mg bolus plus 4 mg/min infusion for 120 minutes) and 55 patients (15.6%) received the high dose regimen (i.e., 800 mg bolus plus 8 mg/min infusion for 120 minutes).

An overall TE events summary by subgroup is provided in Figure A 2. Table A 4 provides a summary of TEs by bleed type, Table A 5 summarises TEs by the type of TE, and Table A 6 provides a comparison between patients experiencing TEs and those not experiencing TEs. Thrombotic event rates in patients with and without re-anticoagulation are provided in Table A 7. Individual types of TEs included DVT, MI, PE, cerebrovascular accident (CVA), and transient ischemic attack (TIA).

FIGURE A 2. THROMBOTIC EVENTS SUMMARY BY SUBGROUP (SAFETY POPULATION)



Database lock date: 28Nov2018. The Safety Population includes all patients who received any amount of andexanet.
The subgroup (missing eGFR) with small numbers of events was excluded.
Thrombotic event and bleed type were adjudicated by the Endpoint Adjudication Committee. Asian, American Indian or Alaska Native, or missing are reported as other.
AF: Atrial Fibrillation, VTE: Venous Thromboembolism, CVA: Stroke Ischemic/Uncertain Classification, DVT: Deep Vein Thromboembolism , MI: Myocardial Infarction, PE: Pulmonary Embolism, TIA: Transient Ischemic Attack
Study: ANNEXA4 (14-505), Program: Figure 14.3.1 2.sas, Output: Figure 14.3.1 2.rtf, Date: 01MAY2019

Of the 352 patients in the Safety Population, 34 (9.7%) reported TEs confirmed by adjudication during follow-up (Table A 4) between the start of andexanet treatment and the Day 30 visit.

Overall, CVAs and DVTs were the most common TEs, both in the overall Safety Population and in patients with ICH. The TE rate was broadly consistent across bleed types and FXa inhibitors, though the analysis was limited by small numbers of TEs in certain subgroups (Figure A 2, Table A 4). The median age of patients with TEs (79 years) was the same as the median age for those without TEs (Table A 4). Most patients with TEs (76.5%) were receiving their FXa inhibitor for a history of atrial fibrillation. However, the percentage of patients receiving an FXa inhibitor for a history of VTE experienced TEs (29.4%) at a higher rate than those

without a prior history of TEs (24.2%). A total of 10 patients had TEs that were considered to be treatment-related by the Investigator (Listing 16.2.7.4).

The median time to first TE event was 10 days after andexanet treatment (Table A 4). The majority (67.6%) of TEs occurred at least 4 days after andexanet administration (Table A 6). Patients initially presenting with ICH had the longest time to event (11 days) (Table A 4).

Taken together, the above data suggest that patients in ANNEXA-4 have a high baseline thrombotic risk based on their age, comorbidities (indication for FXa inhibitor), acute major bleeding status, and level of disability. The median time to event was 10 days, driven largely by patients with ICH (median time to event = 11 days). Consistent with these observations, CVAs and DVTs were the most common type of TE. Accordingly, the background risk profile, level of disability, prolonged length of stay, and delays in re-anticoagulation all represent compelling contributors to the development of TEs.

TABLE A 4. CHARACTERISTICS OF THROMBOTIC EVENTS AND RE-ANTICOAGULATION STRATIFIED BY PRIMARY BLEEDING SITE (SAFETY POPULATION)

	GI	ICH	Other	All Patients
Group	All (N=90)	All (N=227)	All (N=35)	All (N=352)
TE, n(%)	6 (6.7)	21 (9.3)	7 (20.0)	34 (9.7)
Age (years)				
Mean	73.0	81.0	75.4	78.5
Median	73.0	81.0	79.0	79.0
FXa Inhibitor				
Apixaban	2	9	4	15
Rivaroxaban	4	11	2	17
Edoxaban	0	1	0	1
Enoxaparin	0	0	1	1
TE Type[1]				
CVA	1	11	1	13
DVT	0	8	2	10
PE	2	0	2	4
MI	2	2	2	6
TIA	1	0	0	1
Indication for Anticoagulation				
Arterial Thromboembolism	0	0	1	1
Atrial Fibrillation	3	17	5	25
VTE	3	4	3	10
Other	0	0	2	2
Time to First TE (median, days)[2]	6	11	7	10
First TE Onset within				
0-12 hours (inclusive)	2	2	1	5
>12 hours and <4 days	1	3	2	6
4-30 days (inclusive)	3	16	4	23
Number of Patient Re-anticoagulated[3]	2	11	6	19
Within 30 days since TE onset	2	4	5	11
Prior to TE onset	0	7	1	8
Days to Re-anticoagulation (median)	22.5	3.0	13.5	7.0
Hospital Length of Stay (median, days)	2.5	10.7	13.4	8.5

Database lock date: 28Nov2018. The Safety Population includes all patients who received any amount of andexanet.
Thrombotic event and bleed type were adjudicated by the Endpoint Adjudication Committee.
[1] TE type is summarised at subject level. A patient may have multiple TE type.
[2] Time to first TE is includsive of the dosing day.
[3] one patient could have multiple indications for the initial anti-coagulation.
CVA: Stroke Ischemic/Uncertain Classification, DVT: Deep Vein Thromboembolism , MI: Myocardial Infarction, PE: Pulmonary Embolism, TIA: Transient Ischemic Attack
Study: ANNEXA4 (14-505), Program: Table 14.3.2.12.sas, Output: Table 14.3.2.12.rtf, Date: 03MAY2019

TABLE A 5. CHARACTERISTICS OF THROMBOTIC EVENTS STRATIFIED BY TE TYPE [1] (SAFETY POPULATION)

	CVA	MI	DVT[3]	PE[3]	TIA[3]	All Patients
Group	**All**	**All**	**All**	**All**	**All**	**All**
TE, n(%)[2]	14 (4.0)	7 (2.0)	13 (3.7)	5 (1.4)	1 (0.3)	34 (9.7)
Age (years)						
Mean	82.8	80.0	72.7	81.3	60.0	78.5
Median	87.0	81.5	75.5	80.5	60.0	79.0
FXa Inhibitor						
Apixaban	5	5	7	2	0	15
Rivaroxaban	7	2	6	3	1	17
Edoxaban	1	0	0	0	0	1
Enoxaparin	1	0	0	0	0	1
Bleed Type						
GI	2	3	1	2	1	6
ICH	11	2	9	1	0	21
Other	1	2	3	2	0	7
Indication for Anticoagulation						
Arterial Thromboembolism	0	0	0	1	0	1
Atrial Fibrillation	11	6	8	3	0	25
VTE	4	1	5	3	1	10
Other	1	0	1	0	0	2
Time to First TE (median, days)[4]	7	2	14	20	15	10
First TE Onset within						
0-12 hours (inclusive)	2	2	0	1	0	5
>12 hours and <4 days	2	3	1	0	0	6
4-30 days (inclusive)	9	1	9	3	1	23
Number of Patient Re-	5	3	12	5	0	19
Within 30 days since TE onset	5	3	4	3	0	11
Prior to TE onset	0	0	8	2	0	8
Days to Re-anticoagulation (median)	9.5	6.5	4.0	22.5	0	7.0

Database lock date: 28Nov2018. The Safety Population includes all patients who received any amount of andexanet.
[1] TE type is summarised at subject level. A patient may have multiple TE type. Thrombotic event and bleed type were adjudicated by the Endpoint Adjudication Committee.
[2] The denominator is a total number of subjects in the generation.
[3] Generation 2 doesn't have any TE in DVT, PE, or TIA.
[4] Time to first TE is includsive of the dosing day.
[5] A patient could have multiple indications for the initial anti-coagulation.
CVA: Stroke Ischemic/Uncertain Classification, DVT: Deep Vein Thromboembolism , MI: Myocardial Infarction, PE: Pulmonary Embolism, TIA: Transient Ischemic Attack
Study: ANNEXA4 (14-505), Program: Table 14.3.2.9.sas, Output: Table 14 3.2.9.rtf, Date: 03MAY2019

TABLE A 6. COMPARISON OF PATIENTS WITH THROMBOTIC EVENTS VERSUS PATIENTS WITHOUT THROMBOTIC EVENTS (SAFETY POPULATION)

		All Patients (N=352)	
Group	**Statistic**	**With TE (N=34)**	**Without TE (N=318)**
Age (years)	Median	79.0	79.0
FXa Inhibitor, n(%)			
	Apixaban	15 (44.1)	179 (56.3)
	Rivaroxaban	17 (50.0)	111 (34.9)
	Edoxaban	1 (2.9)	9 (2.8)
	Enoxaparin	1 (2.9)	19 (6.0)
Bleed Type, n(%)			
	GI	6 (17.6)	84 (26.4)
	ICH	21 (61.8)	206 (64.8)
	Other	7 (20.6)	28 (8.8)
History, n(%)			
	AF	26 (76.5)	260 (81.8)
	CVA	8 (23.5)	77 (24.2)
	VTE	10 (29.4)	77 (24.2)
	Cancer	9 (26.5)	94 (29.6)
Death, n(%)		10 (29.4)	44 (13.8)
Hospital Length of Stay (days)	Median	8.5	7.1

Database lock date: 28Nov2018. The Safety Population includes all patients who received any amount of andexanet
Thrombotic event and bleed type were adjudicated by the Endpoint Adjudication Committee.
Study: ANNEXA4 (14-505), Program: Table 14.3.2.11.sas, Output: Table 14.3.2.11.rtf, Date: 03MAY2019

Analysis and Discussion of Thrombotic Events

The molecular structure of andexanet is designed to minimise pro-thrombotic activity. While it is an analogue of FXa, it is rendered incapable of cleaving prothrombin to thrombin due to the substitution of alanine for a critical serine residue in the active site that is required for catalytic activity. This replacement results in andexanet having no intrinsic pro-coagulant activity.

This mechanistic consideration has been confirmed in nonclinical toxicology studies in cynomolgus monkeys, where no differences in the occurrence of histopathologic thrombi were seen between animals treated with andexanet (60 mg/kg/day every 3 days for 14 days) and animals treated with vehicle. These data supported a No Observed Adverse Effect Level (NOAEL) of 60 mg/kg/day.

In Phase 1-3 healthy volunteer studies of andexanet, elevations in F1+2 and D-dimer were observed both in the absence (Phase 1) and presence (Phase 2 and 3) of FXa inhibitors. However, the magnitude of elevations was attenuated in the presence of FXa inhibitors. In the nonclinical toxicology study cited above, similar elevations in F1+2 and D-dimer were evident.

In the human Phase 1-3 studies, the elevations of F1+2 and D-dimer were coincident with a parallel decrease in levels of TFPI, an endogenous inhibitor of FXa. As andexanet is known to bind TFPI, this provides a plausible mechanism for these elevations. However, there have been no clinical signs of thrombosis or TEs in healthy subjects in the Phase 1 to 3 studies, and it is uncertain whether the andexanet: TFPI interaction is a significant contributor to the occurrence of TEs in ANNEXA-4, as opposed to other

factors (e.g., background thrombotic risk, acuity of disease, coagulopathic derangement associated with major bleeding).

Patients with acute major bleeding on anticoagulants are at high risk for TEs for two reasons. First, patients prescribed anticoagulants generally have an underlying condition that necessitates their use; these conditions (e.g., atrial fibrillation, venous thromboembolism) are pro-thrombotic in nature. To this end, the FDA-approved product labels for the direct FXa inhibitors that include a warning that premature discontinuation of the anticoagulant in patient populations for whom they are indicated increases the risk of TEs.

Second, patients with acute major bleeding experience alterations in haemostatic parameters that result in a paradoxical pro-thrombotic state, especially when the bleeding is due to traumatic injury [75]. Accordingly, randomised clinical trials and real-world studies have established that major bleeding in patients taking anticoagulants is associated with an increased thrombotic risk. Such studies have reported TE rates of approximately 10% over follow-up periods ranging from hospital discharge to 90 days, though rates as high as 28% have been reported [76-85]. While several studies have lower TE rates compared to this study, they also tend, to varying extents, to enroll populations that are younger [84, 86], have more spontaneous as opposed to anticoagulant related bleeds [78, 81, 82], have fewer ICH patients [54, 84, 86-89], have fewer patients with VTE [76, 80, 86, 88, 89], or have incomplete, unreported, or limited duration of follow-up [17, 79, 80, 84].

With regards to ANNEXA-4, while the observed rate of TEs in the current analysis set is nominally greater than some rates observed in the above studies, it should be noted that the ANNEXA-4 population is generally older, is enriched for ICH patients, and includes approximately 29% of the patients taking FXa inhibitors for venous thromboembolic disease (an indicator of an underlying hypercoagulable state) (Table A 4).

Furthermore, across most of the above studies, the mortality rates are comparable to that observed in ANNEXA-4. Finally, it should be noted that, during the time encompassed by the enrollment of the patients in this report, the DSMB has reviewed cumulative safety data (including TEs from the Safety Population). Following each review, the DSMB has recommended that the study proceed as planned.

In summary, andexanet was purposefully designed to avoid pro-coagulant effects. Nonclinical toxicology studies evaluating high doses of andexanet have indicated a NOAEL of 60 mg/kg/day – greater than double the highest anticipated single-dose clinical exposure. While transient increases in some coagulation biomarkers were observed in healthy volunteer studies, no TEs occurred in these studies. In ANNEXA-4, patients have a high baseline thrombotic risk based on their age, comorbidities, and level of disability, even relative to populations in contemporary studies.

Re-Anticoagulation

Given the potential for TEs in a population of patients with rapid reversal of anticoagulation, the timing and rate of re-anticoagulation was documented for all patients. Rates of TEs in patients with and without resumption of anticoagulation is provided in Table A 7.

The overall rate of re-anticoagulation in the Safety Population was 63.4% (223 patients). The re-anticoagulation rate was lowest in patients with GI bleeding (56.7%), and highest in patients with other (i.e., non-ICH, non-GI) bleeding (82.9%). The re-anticoagulation rate of ICH patients was 63.0%. Of these 223 patients, 105 resumed oral anticoagulation (Table A 8).

As expected for a population of patients with major bleeding and a high underlying thrombotic risk, the rate of TEs in patients that did not resume anticoagulation was approximately two- to three-fold greater than the rate of TEs in patients that were re-anticoagulated (note that for the purposes of calculating TE rates, a patient resuming anticoagulation on the same date or after the TE was considered not to have been re-anticoagulated). Importantly, 8 of 223 patients (2.3%) restarting any anticoagulation (includes single, non-therapeutic dose of heparin, or oral aspirin) experienced a TE after resumption, and no TEs occurred after the resumption of oral anticoagulation, such as warfarin or direct FXa inhibitors (Table A 8).

TABLE A 7. THROMBOTIC EVENTS AND RE-ANTICOAGULATION (SAFETY POPULATION)

			Patients Anticoagulated		
Population	**Bleed Type**	**Patients Not Anticoagulated (n=129)**	**Total**	**Prior to events**	**After events**
All Patients					
Patients With Thrombotic Events (n=34)	All	14 (10.9)	20 (9.0)	12 (60.0)	8 (40.0)
	GI	4 (3.1)	2 (0.9)	2 (100.0)	0
	ICH	9 (7.0)	12 (5.4)	5 (41.7)	7 (58.3)
	Other	1 (0.8)	6 (2.7)	5 (83.3)	1 (16.7)
Patients Without Thrombotic Events	All	115 (89.1)		203	
	GI	35 (27.1)		49 (22.0)	
	ICH	75 (58.1)		131	
	Other	5 (3.9)		23 (10.3)	
Patients Treated With Generation 1		100		136	
Patients With Thrombotic Events (n=25)	All	8 (8.0)	17	9 (52.9)	8 (47.1)
	GI	2 (2.0)	2 (1.5)	2 (100.0)	0
	ICH	5 (5.0)	9 (6.6)	2 (22.2)	7 (77.8)
	Other	1 (1.0)	6 (4.4)	5 (83.3)	1 (16.7)
Patients Without Thrombotic Events	All	92 (92.0)		119	
	GI	29 (29.0)		35 (25.7)	
	ICH	60 (60.0)		69 (50.7)	
	Other	3 (3.0)		15 (11.0)	
Patients Treated With Generation 2		29		87	
Patients With Thrombotic Events (n=9)	All	6 (20.7)	3 (3.4)	3 (100.0)	0
	GI	2 (6.9)	0	0	0
	ICH	4 (13.8)	3 (3.4)	3 (100.0)	0
Patients Without Thrombotic Events	All	23 (79.3)		84 (96.6)	
	GI	6 (20.7)		14 (16.1)	
	ICH	15 (51.7)		62 (71.3)	
	Other	2 (6.9)		8 (9.2)	

Database lock date: 28Nov18. The Safety Population included all patients treated with any amount of andexanet.
Three of 223 patients were treated with an anticoagulant after Day 30.
Thrombotic event and bleed type were adjudicated by the Endpoint Adjudication Committee.
Study: ANNEXA4 (14-505), Program: Table 14.3.2.13.sas, Output: Table 14.3.2.13.rtf, Date: 03MAY2019

TABLE A 8. THROMBOTIC EVENTS (SAFETY POPULATION)

Variable	Bleed Type			All Patients (N = 352)
	GI (N = 90)	ICH (N = 227)	Other (N = 35)	
All Patients				
Patients Re-starting Any Anticoagulation	51 (56.7)	143 (63.0)	29 (82.9)	223 (63.4)
TE Prior to Re-start of Anticoagulation [1]	6 (6.7)	14 (6.2)	6 (17.1)	26 (7.4)
TE After Re-start of Anticoagulation	0	7 (3.1)	1 (2.9)	8 (2.3)
Patients Re-starting of Oral Anticoagulation [2]	42 (46.7)	44 (19.4)	19 (54.3)	105 (29.8)
TE Prior to Re-start of Oral Anticoagulation	6 (6.7)	21 (9.3)	7 (20.0)	34 (9.7)
TE After Re-start of Oral Anticoagulation	0	0	0	0

Based on data transfer from 28NOV18. All patients who received any amount of andexanet are included.
Three of 223 patients were treated with an anticoagulant after Day 30. Thrombotic Event and bleed type were adjudicated by the Endpoint Adjudication Committee.
[1] Included are thrombotic events that occured in patients who never restarted anticoagulation
[2] Restart of oral anticoagulation includes only the use of vitamin K antagonists or non-vitamin K oral anticoagulants (at any dose and for any duration).
Study: ANNEXA4 (14-505), Program: Table 14.3.2.14.sas, Output: Table 14.3.2.14.rtf, Date: 29MAY2019

In general, thrombosis rates in anticoagulated patients who have a bleeding event are substantially higher than those observed in patients who do not experience a bleed. Patients taking apixaban in the ARISTOTLE trial who experienced a major non-ICH or ICH bleed had a 12-fold or 22-fold increased risk, respectively, of MI or stroke within 30 days, compared with patients who did not experience a bleed [90]. Moreover, re-anticoagulation after a major bleed in patients taking warfarin reduces the risk of TEs by 2- to 10-fold, and reduces the risk of death by 3-fold [91, 92].

7.5.2 Comment on the considerations underlying the fact that the ANNEXA-4 trial primarily recruited patients with intracranial haemorrhage

The decision to enrich ANNEXA-4 was subsequent to regulatory discussion to ensure the population with the greatest potential mortality and morbidity benefit was preferentially reflected in the study and to ensure assessment of haemostatic efficacy was based on the most objectively determined clinically relevant criteria (i.e. haematoma expansion through centralised CT imaging determination as per Sarode et al. criteria (Table A 9).[29]

TABLE A 9. RATING SYSTEM FOR EFFECTIVE HEMOSTASIS

Bleed Type	Excellent (effective)	Good (effective)	Poor/none (not effective)
Visible	Cessation of bleeding ≤ 1 hour after end of infusion and no plasma, coagulation factor or blood products (excludes pRBCs).[1]	Cessation of bleeding between > 1 and ≤ 4 hours after end of infusion and ≤ 2 units plasma, coagulation factor or blood products (excludes pRBCs).[4]	Cessation of bleeding > 4 hours after end of the infusion and /or >2 units plasma, coagulation factor or blood products (excludes pRBCs).[5]
Muscular/skeletal	pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding ≤1 hour after the end of infusion; and the condition has not deteriorated during the 12-hour period	pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding >1 and ≤4 hours after end of infusion; and the condition has not deteriorated during the 12-hour period	No improvement by 4 hours after end of infusion and/or condition has deteriorated during the 12-hour period
Intracerebral hematoma	≤20% increase in hematoma volume compared to baseline on a repeat CT or MRI scan performed at both the 1 and 12 hour post infusion time points	>20% but ≤35% increase in hematoma volume compared to baseline on a repeat CT or MRI scan at +12-hour time point	>35% increase in hematoma volume on a CT or MRI compared to baseline on a repeat CT or MRI scan at +12-hour time point
Subarachnoid bleed	≤20% increase in maximum thickness using the most dense area on the follow-up vs baseline at both the 1 and 12 hour post infusion time points	>20% but <35% increase in maximum thickness using the most dense area on the follow-up at +12h vs baseline	>35% increase in maximum thickness using the most dense area on the +12h vs at baseline
Subdural hematoma	≤20% increase in maximum thickness at both the 1 and 12 hour post infusion assessments compared to baseline	>20% but < 35% increase in maximum thickness at +12h compared to baseline	>35% increase in maximum thickness at +12h compared to baseline
Pericardial	No increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion	<10% increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion	10% or more increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion
Intra-spinal	No increase in hematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion	<10% increase in hematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion	10% or more increase in hematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion
GI, Urinary or non-visible bleeding not described above	≤10% decrease in both corrected hemoglobin/hematocrit at 12 hours[2,3] compared to baseline	>10 % to ≤20% decrease in both corrected hemoglobin/hematocrit at 12 hours compared to baseline[2,3]	>20% decrease in both corrected hemoglobin/hematocrit[2,3]

Additional Factors to be Considered During Adjudication

1. Any additional diagnostic data for a particular bleeding site (e.g., nasogastric tube, ultrasound, GI endoscope, echocardiogram, or CT/MRI scans) will be taken into account for the overall assessment.
2. Any uncontrolled bleeding that did not respond to andexanet and was related to an underlying disease will be taken into account for the overall assessment.
3. Pain, swelling, and signs of bleeding are considered to be typical symptoms of musculoskeletal bleeding and are expected to be present at baseline.

[1]For all types of bleeding: no additional plasma, blood products (whole blood products not including packed red blood cells [PRBCs]) and/or coagulation factor products required after initial treatment with andexanet.

[2]The smallest percentage decrease in hemoglobin or hematocrit should be used to determine the efficacy rating of excellent, good, or poor/none. The net change is defined as the difference between the corrected hemoglobin or hematocrit value at baseline and 12 hours after infusion

[3] For the adjusted hemoglobin and hematocrit calculation, it will be assumed that for each unit of PRBC transfusion there is an increase of 1 g/dL in hemoglobin and a 3% increase in hematocrit.

[4]For all types of bleeding, no more than two additional units of plasma or blood products and/or coagulation factor products required after initial treatment with andexanet. "Blood products" include whole blood but not PRBCs.

[5]For all types of bleeding, more than two additional units of plasma or blood products and/or coagulation factor products required after initial treatment with andexanet. "Blood products" include whole blood but not PRBCs.

Consequently, protocol amendment 4 resulted in the following changes impacting enrollment criteria:

- Increased sample size from 250 patients to 350 patients.
- Enriched patient population for ICH; ensured a minimum of 110 efficacy evaluable ICH patients, including 50 patients at high risk for haematoma expansion.
- Added a requirement for a reasonable expectation that a patient would be treated with andexanet within 2 hours after a baseline scan (ICH patients only).
- Excluded patients with visible, intra-articular, and musculoskeletal bleeding.
- Excluded patients for whom the investigator believed that the haemoglobin would drop below 8 g/dL after volume resuscitation.

A phase 4 randomised clinical trial of andexanet alfa in acute intracranial haemorrhage in patients receiving oral factor Xa inhibitor NCT03661528 (ANNEXA-I) is a specific post authorisation obligation specified as part of additional risk minimization activity. The objective of ANNEXA-I is to substantiate correlation of the biomarker (anti-FXa activity) with haemostatic efficacy and clarify the risk of thromboses and thromboembolic events. Portola are committed to the completion of ANNEXA-I which is a global randomised controlled clinical trial to investigate the use of andexanet versus standard of care treatment in patients with intracranial haemorrhage taking apixaban, rivaroxaban, or edoxaban. Current EMA submission of final CSR is planned for 2023. The requirement for ANNEXA-I stems from the following uncertainties as described in the EPAR:

- Correlation of the biomarker (anti-FXa% change from baseline) with haemostatic efficacy is not established. As the clinical development concept is based upon anti-FXa-activity to represent the clinical effect for reversing anti-fXa effects induced by DOACs (mode of action).

- A risk of thromboses and thromboembolic events has been identified with the treatment of andexanet. This potential risk may involve patients on high-dose andexanet, patients on rivaroxaban and patients on lower dose anticoagulant-regimen prior to the bleeding event. Currently missing information relates to safety as regards the risk of thromboembolic events relative to a concurrent control population that does not receive andexanet.

ANNEXA-4 included the following eligibility criteria.

Inclusion criteria:

1. Either the patient or his or her medical proxy has been adequately informed of the nature and risks of the study and has given written informed consent prior to Screening
2. The patient must be at least 18 years old at the time of Screening
3. The patient must have an acute overt major bleeding episode requiring urgent reversal of anticoagulation; acute major bleeding requiring urgent reversal of anticoagulation is defined by at least ONE of the following:
    - Acute overt bleeding that is potentially life-threatening, e.g., with signs or symptoms of haaemodynamic compromise, such as severe hypotension, poor skin perfusion, mental confusion, low urine output that cannot be otherwise explained;
    - Acute overt bleeding associated with a fall in haemoglobin level by ≥2 g/dL, OR a Hb ≤ 8 g/dL if no baseline Hb is available OR, in the opinion of the investigator that the patient's haemoglobin will fall to ≤ 8 g/dL with resuscitation;
    - Acute symptomatic bleeding in a critical area or organ, such as, retroperitoneal, intra-articular or pericardial, intracranial or intramuscular with compartment syndrome.
4. The patient, for whom the bleeding is intracranial must have undergone a head CT or MRI scan demonstrating the intracranial bleeding. Note: Patients with bleeding at non-intracranial locations do not require a head CT or MRI
5. Patient received or believed to have received one of the following within 18 hours prior to andexanet administration: apixaban, rivaroxaban, edoxaban or enoxaparin (dose of enoxaparin ≥1 mg/kg/d)

Exclusion criteria:

1. The patient is scheduled to undergo surgery in less than 12 hours with the exception of minimally invasive surgery/procedures
2. A patient with ICH has any of the following:
   Glasgow coma score < 7
   Estimated intracerebral haematoma volume >60 cc as assessed by the CT or MRI
3. The patient has an expected survival of less than 1 month
4. The patient has a recent history (within 2 weeks) of a diagnosed thrombotic event (TE) as follows: myocardial infarction, disseminated intravascular coagulation (DIC), cerebral vascular accident, transient ischemic attack, unstable angina pectoris hospitalization, or severe peripheral vascular disease within 2 weeks prior to Screening
5. The patient has severe sepsis or septic shock at the time of Screening
6. The patient is pregnant or a lactating female
7. The patient has received any of the following drugs or blood products within 7 days or Screening: a) Vitamin K antagonist (VKA) (e.g., warfarin) b) Dabigatran c) Prothrombin Complex Concentrate products (PCC, e.g., Kcentra®) or recombinant factor VIIa (rfVIIa) (e.g., NovoSeven®) d) Whole blood, plasma fractions
   (Note: Administration of platelets or packed red blood cells (PRBCs) is not an exclusion criterion);
8. The patient was treated with an investigational drug <30 days prior to Screening
9. Planned administration of PCC, fresh frozen plasma (FFP), or rfVIIa from Screening until within 12 hours after the end of the andexanet infusion
10. The study enrolled patients who had recently taken a fXa inhibitor (i.e., within 18 hours or at an unknown time) and whom present with an acute major bleeding episode. The definition of major bleeding is based on the ISTH definition and is very similar to that used in the study by Sarode, et al. Slight modifications have been made to the definition of major bleeding in order to provide further detail on circumstances for which the use of a reversal agent would be deemed medically necessary. Importantly, to ensure that only patients with a severe, uncontrollable and life-threatening bleeding of acute presentation are enrolled, only patients who urgently require reversal of anticoagulation are eligible. Patients who are candidates for “watchful waiting” with respect to anticoagulation reversal would not be eligible based on the entry criteria. To ensure uniformity of application of the bleeding entry criteria, and external adjudication committee (EAC) reviewed source documents to determine eligibility based upon this criterion. This eligibility review occurred before reviewers were given access to post-baseline data. Patient eligibility, based on the central review, determined whether or not patients are included in the Efficacy Analysis Population; however, because central reviews did not occur in real time, the central review decisions did not affect enrollment of patients.

In addition, because there is no standardised clinical assay for anti-fXa activity, it was not possible to use anti-fXa activity as a marker of anticoagulation for purposes of enrollment. However, samples for anti-fXa activity were collected at baseline and post-baseline for later analysis at a central laboratory. As a surrogate for elevated anti-fXa activity, the eligibility criteria restrict enrollment to patients who received their last dose of fXa inhibitor within 18 hours. The 18-hour time point was selected to enrol the maximum number of patients while avoiding enrolling a large number of patients who are inevaluable for the primary efficacy analysis due to low anti-fXa activity levels. The 18-hour time point is the approximate time, following a dose of rivaroxaban, to a plasma concentration that is approximately equal to twice the mean trough level at 24 hours. Therefore, it is likely that bleeding occurring within this 18-hour window is the result of fXa inhibition or aggravated by fXa inhibition. The Efficacy Analysis Population for the study will only include patients whose central laboratory determined anti-fXa activity is >75 ng/mL.

In order to enrol a population that will be similar to the intended target population for andexanet, the eligibility criteria had few restrictions on comorbid conditions. For example, there was no upper age limit or lower limit for renal function. There were also no restrictions on concomitant medications, other than medicines which could either potentially result in increased thromboembolic risk or confound efficacy assessment. Patients with known selected hypercoagulable states and recent thrombotic events (TEs) (i.e., within 2 weeks) were excluded because of their increased risk for TEs, especially if anticoagulation is reversed. Furthermore, antibodies to coagulation factors may interfere with the thrombin generation assay or fXa assay being used in this study. Finally, patients who have received procoagulant products (e.g., PCC, rFVIIa) within 7 days are also excluded because of their higher risk of TE.

In summary, the eligibility criteria for ANNEXA-4 was developed with agreement from the EMA to encompass the licensed indication of adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Furthermore, it also incorporated the need for the clinical development program to elucidate acute haemostatic efficacy in the clinical population most likely to benefit (evolving with enrichment of ICH patient population) and characterisation of acute and longer term (30 day) safety profile of andexanet for marketing registration purposes.

7.5.3 Separated efficacy estimates from the ANNEXA-4 trial by site of bleeding

All deaths that occurred during the 30-day safety follow-up period were adjudicated by the EAC. Of the 352 patients completing 30-day safety follow-up, there were 54 deaths (15.3%) occurring prior to the Day 30 visit (Table A 10). The numbers of cardiovascular and non-cardiovascular deaths were 37 (68.5% of deaths) and 12 (22.2%), respectively (the etiology for 5 deaths were uncertain or unknown) (Listing 16.2.7.5b).

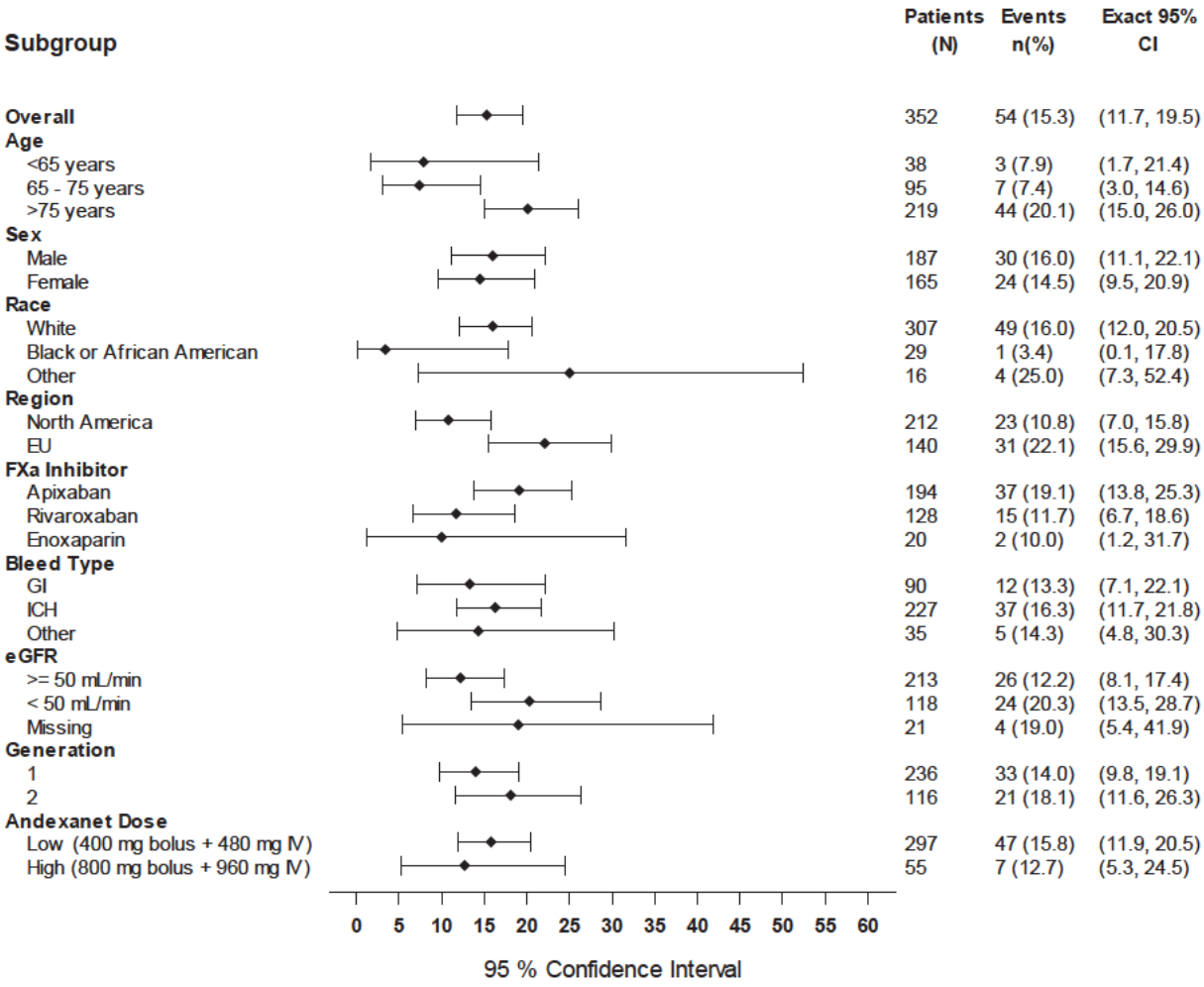
TABLE A 10. ADJUDICATED REASON FOR DEATH (SAFETY POPULATION)

Reasons for Death	Generation 1	Generation 2	All Patients
All Patients	33 (14.0)	21 (18.1)	54 (15.3)
Cardiovascular	19 (8.1)	18 (15.5)	37 (10.5)
Non-Cardiovasc	10 (4.2)	2 (1.7)	12 (3.4)
Uncertain	2 (0.8)	1 (0.9)	3 (0.9)
Unknown[1]	2 (0.8)	0	2 (0.6)

Database lock date: 28Nov2018. The Safety Population includes all patients who received any amount of andexanet.
[1] Deaths of two patients were not adjudicated.
Study: ANNEXA4 (14-505), Program: Table 14.3.2.1a.sas, Output: Table 14.3.2.1a.rtf, Date: 17MAY2019

The median time to death was 13.5 days (range 1-44); note that 2 deaths occurring between Study Days 30 and 45 occurred prior to the implementation of Amendment 2, during which the safety follow-up interval was decreased from 45 to 30 days. The number of patients dying within 30 days of enrollment was 49 (13.9%). The death rates in patients with GI bleeding and patients with ICH were 13.3% (12/90) and 16.3% (37/227), respectively.

FIGURE A 3. MORTALITY SUMMARY BY SUBGROUP (SAFETY POPULATION)



Database lock date: 28Nov2018. The Safety Population includes all patients who received any amount of andexanet.
The subgroup (Endoxaban) with no death was excluded.
Bleed type was adjudicated by the Endpoint Adjudication Committee. Asian, American Indian or Alaska Native, or missing are reported as other.
Study: ANNEXA4 (14-505), Program: Figure 14.3.1.1.sas, Output: Figure 14.3.1.1.rtf, Date: 01MAY2019

7.5.4 Statement regarding duration of action, including the need for further supportive treatment when using andexanet alfa

Andexanet alfa (andexanet) is a modified, catalytically inactive, recombinant human FXa decoy protein that lacks pro- or anticoagulant activity of its own but retains the ability to bind and sequester FXa inhibitors, thereby restoring activity of native FXa.

The pharmacodynamic profile of andexanet in subjects based on licensed dosing and posology is best characterised in studies ANNEXA-A/R and for bleeding patients in ANNEXA-4.

ANNEXA-A/R

ANNEXA-A and ANNEXA-R trials were randomised, double-blind, placebo-controlled studies that were designed to evaluate the ability of andexanet to reverse anticoagulation with apixaban (Eliquis; Pfizer and Bristol-Myers Squibb) or rivaroxaban (Xarelto; Bayer and Johnson & Johnson) and to evaluate the safety of andexanet in healthy older volunteers.

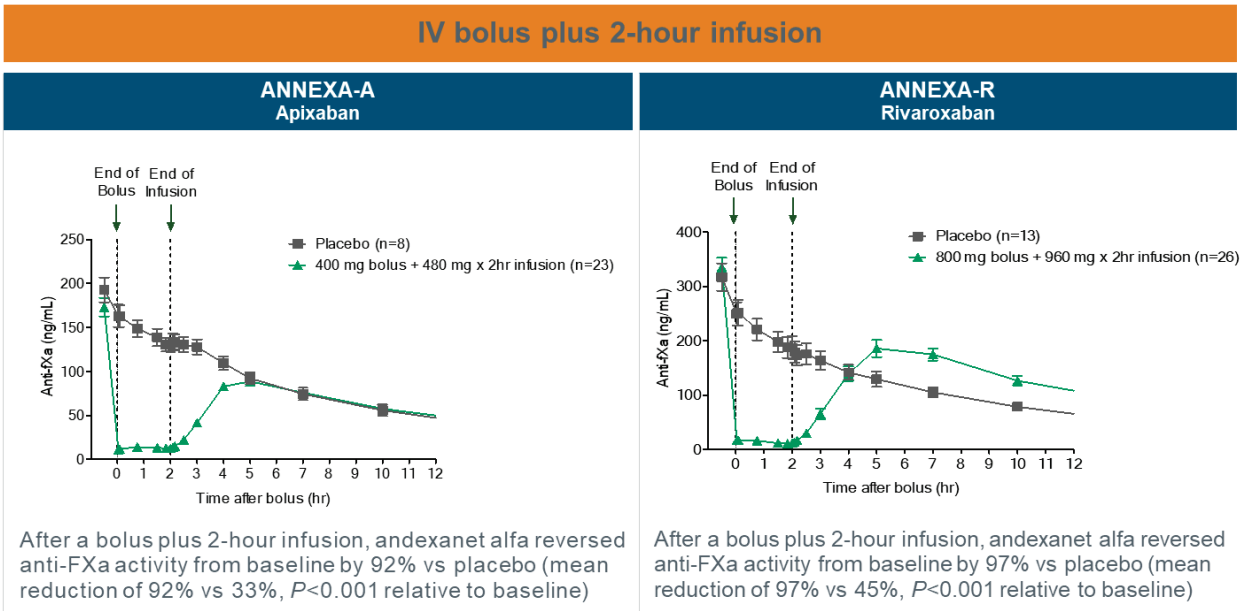
Healthy volunteers 50 to 75 years of age were randomly assigned, with the use of an interactive Web-response system, in a 3:1 ratio (ANNEXA-A) or a 2:1 ratio (ANNEXA-R), to receive andexanet or matching placebo. Each study was performed in two consecutive parts: in part 1, we examined the intravenous andexanet bolus alone, and in part 2 we studied an intravenous bolus followed by a continuous 120-minute infusion. Study participants were housed at the study site for 8 days, and safety outcomes were assessed on days 15, 36, and 43 after administration of the study drug.

In the ANNEXA-A study, participants received 5 mg of apixaban orally twice daily for 3.5 days to achieve steady-state plasma levels at the highest approved dose. Three hours after the last dose of apixaban on day 4 (at or near the time of the highest plasma concentration), andexanet was administered as a 400-mg intravenous bolus (30 mg per minute) (part 1) or as a 400-mg intravenous bolus followed by a continuous infusion of 4 mg per minute for 120 minutes (480 mg in total) (part 2). In the ANNEXA-R study, participants received 20 mg of rivaroxaban orally once daily (the highest approved dose) for 4 days. On day 4, at 4 hours after the last dose of rivaroxaban (at or near the maximum plasma concentration), andexanet was administered as an 800-mg intravenous bolus (30 mg per minute) (part 1) or as an 800-mg intravenous bolus followed by a continuous infusion of 8 mg per minute for 120 minutes (960 mg in total) (part 2).

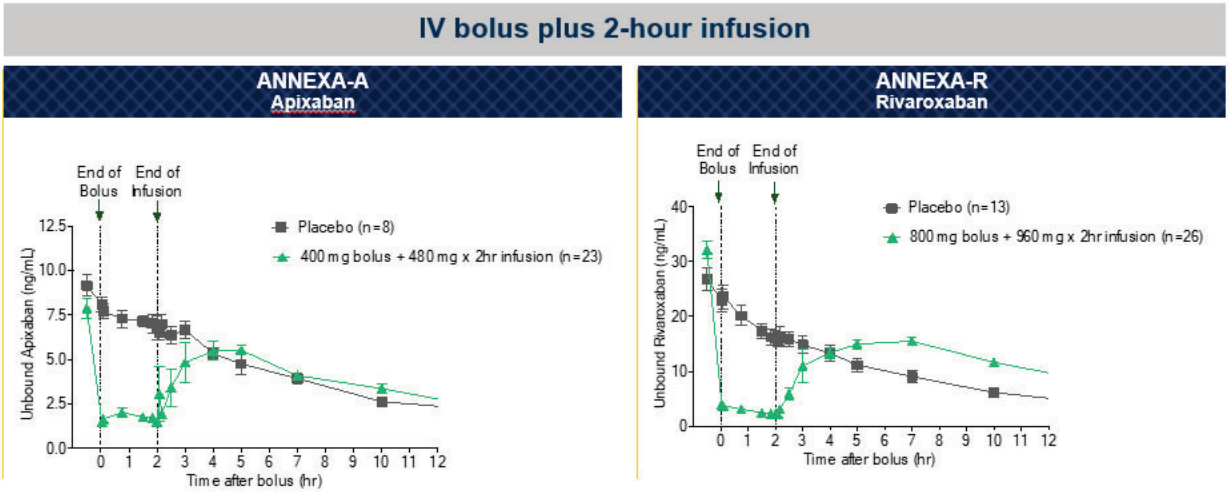
The primary end point for both studies was the percent change in anti–factor Xa activity, measured with the use of a validated chromogenic assay of factor Xa enzymatic activity, from baseline (before administration of andexanet or placebo) to nadir (after administration of andexanet or placebo).

The secondary efficacy end points were the proportion of participants with an 80% or greater reduction in anti–factor Xa activity from baseline to the nadir after administration of andexanet or placebo; the change in unbound inhibitor plasma concentration from baseline to the nadir after administration of andexanet or placebo; the change in thrombin generation, measured as the change in endogenous thrombin potential, from baseline to peak after administration of andexanet or placebo; and the occurrence of an endogenous thrombin potential above the lower limit of the baseline-derived range at its peak after administration of andexanet or placebo (between 2 and 10 minutes after the end of the bolus) or after the infusion.

When andexanet was administered as a bolus plus a 2-hour infusion, it also reduced anti–factor Xa activity to a greater extent than did placebo, both in the apixaban study (92±3% vs. 33±6%, P<0.001) and in the rivaroxaban study (97±2% vs. 45±12%, P<0.001). Among participants who received placebo, anti–factor Xa activity decreased over time at the expected rate for clearance of the anticoagulant. The reversal of anti–factor Xa activity with andexanet persisted for 1 to 2 hours after completion of the infusion, depending on the anticoagulant received, followed by a return to placebo levels. All the participants who were treated with andexanet had at least 80% reversal of anti–factor Xa activity, with the exception of one participant who did not receive the full dose of andexanet because of a malfunction with the intravenous administration; none of participants who received placebo had an 80% or greater reversal of anti–factor Xa activity (P<0.001).

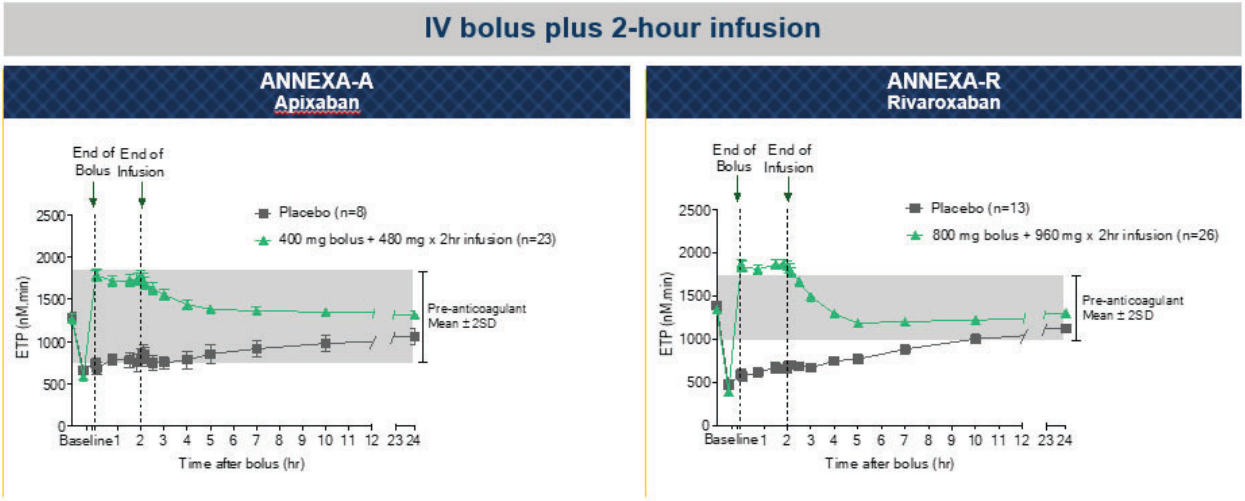


This reversal was sustained with a bolus plus an infusion of andexanet; the mean plasma concentrations of unbound apixaban and rivaroxaban were reduced by a significantly greater amount with andexanet than with placebo (apixaban reduction, 6.5 ng per milliliter vs. 3.0 ng per milliliter, P<0.001; rivaroxaban reduction, 30.3 ng per milliliter vs. 12.1 ng per milliliter, P<0.001). The mean concentration of unbound apixaban after andexanet administration was below 3.5 ng per milliliter, and that of unbound rivaroxaban was below 4.0 ng per milliliter — calculated levels at which there is little or no anticoagulant effect. After the end of the bolus or the infusion of andexanet, the concentrations of unbound factor Xa inhibitor returned to placebo levels within 1 to 3 hours, depending on the anticoagulant.



After administration of bolus plus infusion, the mean change in thrombin generation was significantly greater among participants who received andexanet than among those who received placebo, both in the apixaban study (1193.1±263.3 nM · min vs. 189.4±184.8 nM · min, P<0.001) and in the rivaroxaban study (1510.4±344.8 nM · min vs. 264.4±140.7 nM · min, P<0.001). Among these participants, andexanet restored thrombin generation (to above the lower limit of the normal range) in all the participants in the apixaban study and in the rivaroxaban study; among participants who received placebo, thrombin generation was

restored in 25% of participants in the apixaban study and in no participants in the rivaroxaban study (P<0.001 vs. placebo for each comparison).

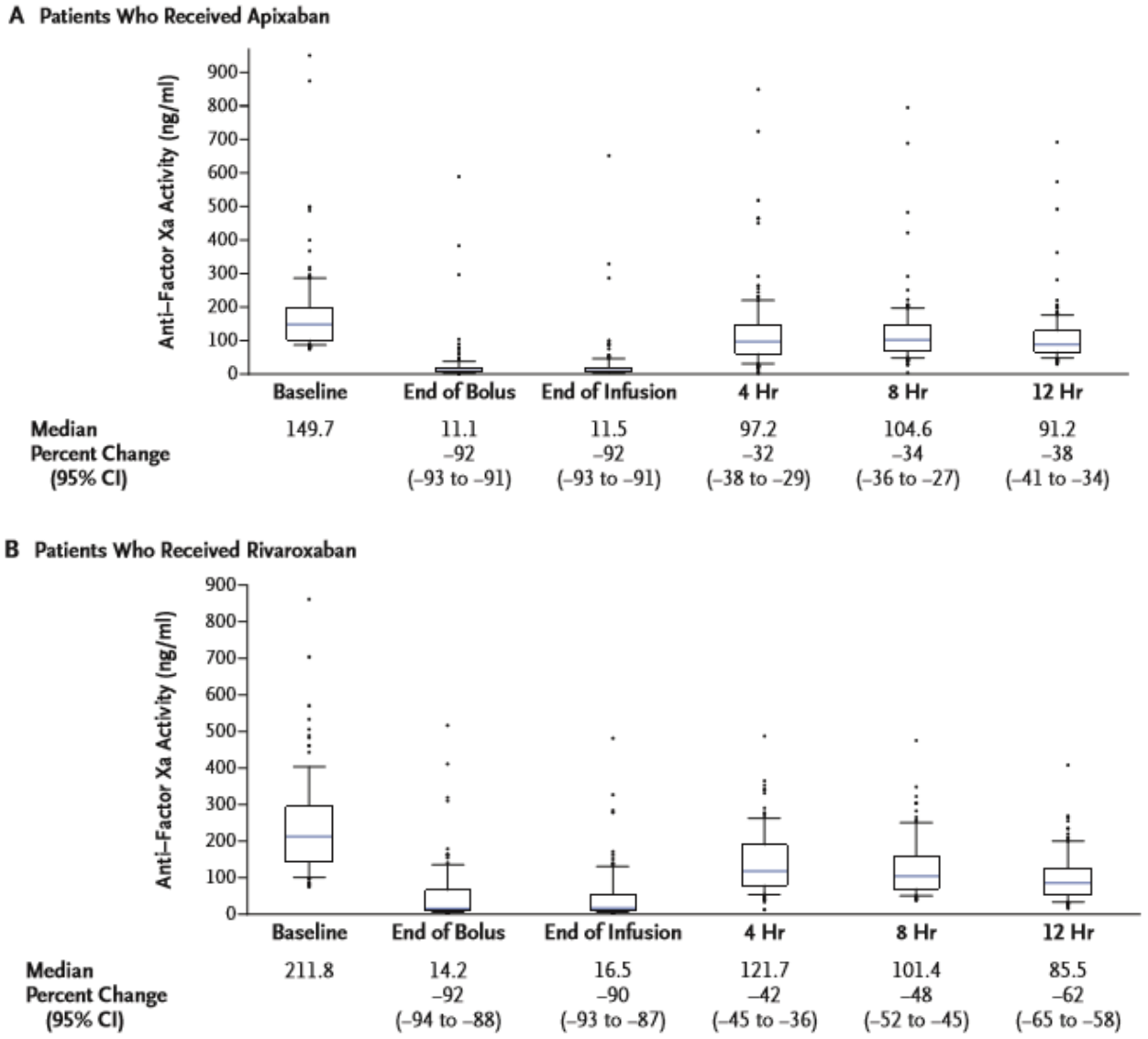


ANNEXA-4

ANNEXA-4 is a Phase IIIb/IV multicenter, prospective, open-label, single-group study. Patients were enrolled at 63 centers in North America and Europe.

The study had two co-primary efficacy outcomes: the percent change from baseline in anti–factor Xa activity after andexanet treatment and the percentage of patients with excellent or good haemostatic efficacy 12 hours after the andexanet infusion, with haemostatic efficacy assessed by an independent adjudication committee on the basis of prespecified criteria.

In the efficacy population, among the 134 patients who were receiving apixaban, the median value for anti–factor Xa activity was reduced from 149.7 ng per milliliter at baseline to 11.1 ng per milliliter at the end of the bolus administration, a 92% reduction (95% confidence interval [CI], 91 to 93). Among the 100 patients who were receiving rivaroxaban, the median value for anti–factor Xa activity fell from 211.8 ng per milliliter at baseline to 14.2 ng per milliliter at the end of the bolus administration, a 92% reduction (95% CI, 88 to 94). At 4, 8, and 12 hours after andexanet infusion, the median value for anti–factor Xa activity was reduced from baseline by 32%, 34%, and 38%, respectively, for apixaban and by 42%, 48%, and 62%, respectively, for rivaroxaban.



Of the 254 patients in the efficacy analysis, 249 could be evaluated for haemostatic efficacy, and 204 (82%) were adjudicated as having excellent or good haemostatic efficacy at 12 hours (95% CI, 77-87). Of these, 171 were adjudicated as having excellent haemostatic efficacy and 33 as having good haemostatic efficacy.

Information on protocol permitted or restrictions on supportive treatment

Other than the prohibited medications stated as part of the exclusion criteria, ANNEXA-4 subjects were prohibited from the planned administration of PCC, FFP, or rfVIIa from Screening until within 12 hours after the EOI.

Additionally, anticoagulant and antiplatelet drugs (e.g., clopidogrel, aspirin, and non-steroidal anti-inflammatory drugs [NSAIDs]) were avoided from the signing of the informed consent form until after the 12-hour haemostatic efficacy evaluation measurements were made.

To maintain uniformity in transfusion practices across study participants, it was strongly suggested that the trigger for PRBC transfusion be a Hb ≤ 8.0 g/dL (± 1 g/dL). The Hb triggering a transfusion, clinical stability

factors (e.g., shock) influencing the decision to transfuse, as well as number of units transfused, were recorded on the CRFs.

Patients were excluded from the study if there was planned use of pro-coagulant factor infusions (e.g., 3- or 4-factor PCC/activated PCC, rfVIIa, plasma, FFP) within 12 hours after the EOI.

Additionally, pro-coagulant infusions and whole blood transfusions were to be avoided starting with the signing of the ICF until after the 12-hour haemostatic efficacy evaluation measurements were made, unless it was required for medical management of the patient.

Platelet transfusions were administered according to standard institutional/local practices and/or guidelines.

Use of blood products, including number of units transfused and the date and time of administration, were recorded on the case report forms (CRFs).

Haemostatic Agents Systemic anti-fibrinolytic (e.g., aminocaproic acid, tranexamic acid) and other systemic haemostatic agents were administered according to standard institutional/local practices and/or guidelines.

Local haemostatic agents (e.g., microfibrillar collagen, chitosan-containing products) and topical vasoconstrictors (e.g., epinephrine) were used as deemed clinically appropriate.

Use of haemostatic agents, their dose, and the date and time of administration were recorded on the CRFs.

Red blood cell transfusions, non-study-prescribed blood products and haemostatic agents

Of the 352 patients in the Safety Population who completed the 30-day safety follow-up, 77 (21.9%) received red blood cell transfusions during the efficacy evaluation period. Of the 77 patients who received a transfusion, the majority were those with a GI bleed (58 patients, 75.3%).

Of the 254 patients in the Efficacy Population, 22 (8.7%) received non-study-prescribed blood products and/or haemostatic agents between the start of andexanet treatment and 12 hours after the end of the infusion. Thirteen patients received a coagulation factor transfusion, 5 patients received haemostatic treatments, and 4 patients received other blood coagulation products. Perhaps consistent with the fact that these patients received the supplemental therapies mentioned above, only 3 patients had a haemostatic efficacy rating of excellent, 7 patients had a rating of good, and 10 had a rating of poor/none (2 patients were non-evaluable).

TABLE A 11. BLOOD PRODUCT USE (ML) AND NON-RBC BLOOD PRODUCT USE OF PATIENTS WITH APIXABAN OR RIVAROXABAN (SAFETY POPULATION)

	All Patients (N=322)	Patients with ICH (N=209)	Patients with GI (N=82)
Blood Product Use (mL)			
Before Andexanet Dosing (N)	62	0	55
Mean (SD)	408.5 (216.80)		397.0 (194.72)
Median	337.3		334.5
IQR	300 - 350		300 - 350
Range	236 - 1240		236 - 1200
0-16 hour (N)	44	2	36
Mean (SD)	366.9 (121.40)	325.0 (35.36)	368.5 (128.57)
Median	330.5	325.0	330.5
IQR	300 - 350	300 - 350	300 - 375
Range	247 - 900	300 - 350	247 - 900
>16 hour (N)	28	5	19
Mean (SD)	398.8 (156.17)	415.0 (96.18)	402.1 (180.72)
Median	350.0	400.0	350.0
IQR	300 - 475	350 - 500	300 - 450
Range	250 - 1000	300 - 525	250 - 1000
Coagulation Factor Transfusion (N)			
Before Andexanet Dosing	8	7	1
30 minutes before end of infusion	5	3	1
1 hour	2	1	1
4 hour	7	6	1
8 hour	3	2	1
12 hour	3	1	2
Haemostatic Treatments (N)			
Before Andexanet Dosing	3	1	2
30 minutes before end of infusion	1	0	0
1 hour	1	0	1
4 hour	2	1	1
8 hour	2	0	1
12 hour	1	0	0
Other Blood/Coagulation (N)			
Before Andexanet Dosing	2	0	1
30 minutes before end of infusion	2	2	0
1 hour	1	1	0
4 hour	1	1	0
12 hour	1	1	0

Database lock date: 28Nov2018. The Safety Population included patients treated with any amount of andexanet. Bleed type was adjudicated by the Endpoint Adjudication Committee. 16 hours is 12 hours after EOI.
Source: Portola data on file[93]

TABLE A 12. BLOOD PRODUCTS AND HAEMOSTATIC AGENTS USE OF PATIENTS RECEIVED APIXABAN OR RIVAROXABAN AFTER ANDEXANET TREATMENT (SAFETY POPULATION)

Group	Blood Products Haemostatic Agents	All Patients (N=322) n (%)
Coagulation Factor Products	4-Factor PCC	4 (1.2)
Blood products	Fresh Frozen Plasma	3 (0.9)
	Plasma	1 (0.3)
	Platelets	22 (6.8)
Haemostatic Treatment	Aminocaproic Acid	1 (0.3)
	Tranexamic Acid	10 (3.1)
Other	Thrombin	2 (0.6)

Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet. Study: ANNEXA-4 (14-505), Program: Table A11.sas, Output: Table A11.rtf, Date: 24OCT2019

7.5.5 Preparation time of andexanet alfa

The preparation time for andexanet alfa is envisaged to be about 20 minutes (depending on familiarity of course).

In section 6.6 in the SmPC [94] the handling of andexanet alfa is described in detail.

Reconstitution

The following are needed before starting reconstitution:

- Calculated number of vials.
- Same number of 20 mL (or larger) solvent syringes equipped with a 20 gauge (or larger) needle.
- Alcohol swabs.
- Large (60 mL or larger) sterile syringe. If a syringe driver is used for administration, multiple syringes should be used to contain the final volume of reconstituted product.
- Intravenous PO or PVC bag (150 mL or larger) to contain the final volume of reconstituted product (if administration is performed with an IV bag).
- Water for injections

Andexanet alfa does not need to be brought to room temperature before reconstitution or administration to the patient. Aseptic technique during the reconstitution procedure should be used.

Each vial is reconstituted according to the following instructions:

1. Remove the flip-top from each vial.
2. Wipe the rubber stopper of each vial with an alcohol swab.
3. Using a 20 mL (or larger) syringe and a 20 gauge (or larger) needle, withdraw 20 mL of water for injections.
4. Insert the syringe needle through the centre of the rubber stopper.
5. Push the plunger down to slowly inject the 20 mL of water for injections into the vial, directing the stream toward the inside wall of the vial to minimise foaming.
6. Gently swirl each vial, until all of the powder is completely dissolved. DO NOT SHAKE the vials, as this can lead to foaming. The dissolution time for each vial is approximately three to five minutes.
7. The reconstituted solution should be inspected for particulate matter and/or discolouration

prior to administration. Do not use if opaque particles or discolouration are present.
8. For the most efficient reconstitution of the needed dose, and to minimise errors, inject each vial needed with 20 mL of water for injections before proceeding to the next step.
9. Use within eight hours after reconstitution when stored at room temperature.

Administration using a syringe pump:
1. Once all required vials are reconstituted, the reconstituted solution is withdrawn from each vial, using the large volume (60 mL or larger) syringe equipped with a 20 gauge (or larger) needle.
2. The bolus and infusion are prepared in separate large volume syringes.
3. Due to the additional volume, the high dose bolus and infusion have to be further separated into additional syringes (two syringes apiece for bolus and infusion).
4. To prevent the inadvertent transfer of air, be careful to hold the syringe needle up, and do not set the syringe down between multiple withdrawals from vials.
5. Attach ancillary equipment (i.e., extension tubing, air filters, syringe driver) in preparation for administration.
6. Administer the reconstituted solution at the appropriate rate.
7. Discard all used syringes, needles, and vials, including any unused portion of reconstituted solution.

Administration using an intravenous bag:
1. Once all required vials are reconstituted, withdraw the reconstituted solution from each vial, using the large volume (60 mL or larger) syringe equipped with a 20 gauge (or larger) needle.
2. Transfer the reconstituted solution from the syringe into an appropriate IV bag.
3. Repeat steps 1 and 2 as necessary to transfer the complete volume of the bolus and the infusion into an IV bag.
4. While it is permissible to combine the bolus and infusion into a single IV bag, it is recommended that the bolus and infusion be split into two separate bags to ensure the correct administration rate.
5. Attach ancillary equipment (i.e., extension tubing, air filters, IV pump) in preparation for administration.
6. Administer the reconstituted solution at the appropriate rate.

Disposal
All used syringes, needles, and vials, including any unused portion of reconstituted solution, should be disposed of in accordance with local requirements.

Ondexxya® (andexanet alfa) for reversal of anticoagulation with factor Xa-inhibitors

Technical document for the health economic analysis

Content

1. Introduction

Andexanet alfa (Ondexxya®) is a modified recombinant inactive form of human factor Xa (FXa) developed for reversal of factor FXa inhibitors. [1] Andexanet alfa is currently the only approved FXa reversal agent. The indication for this product is adult patients treated with a direct FXa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. [2]

Andexanet alfa binds directly to FXa inhibitors with high affinity and does thereby make them unavailable to exert their anticoagulant effects. The predominant mechanism of action for andexanet alfa is the binding and sequestration of the FXa inhibitor, although there may be a minor contribution from the inhibition of tissue factor pathway inhibitor (TFPI) activity through binding to TFPI. The interaction between TFPI and andexanet alfa has not been fully characterized. [2]

1.1. Dose

The recommended dose of andexanet alfa is based on the dose of the FXa inhibitor the patient is taking at the time of anticoagulation reversal, and the time since the last dose of the FXa inhibitor. [2] The distribution of patients receiving high and low dose differs in the protocol and in the main study used in this analysis. [1] [3] As a result, two different distributions of the dosing regimen will be illustrated in this analysis - one as the base case analysis and the other one in a sensitivity analysis.

2. Background

2.1. Patient population

Andexanet alfa is for patients with uncontrolled or life-threatening bleeding who are anticoagulated with the use of a FXa inhibitor. It is estimated that approximately 80.000 patients currently are treated with FXa inhibitors in Denmark, and it is estimated that only a small proportion of the 80.000 will develop a serious acute major bleeding. [3]

Patients included in the analysis are based on the population in the ANNEXA-4 study. The patients in ANNEXA-4 study are from 63 centres in North America and Europe, including northern European countries as Germany, Belgium, and the UK. The study population is considered representative for Danish patients, and the baseline characteristics from this study population was used as baseline characteristics in this health economic analysis for both the SoC and andexanet alfa population. The mean age of the population in this study was 77 years of age and the percentage of females was 47 %. [1]

The ANNEXA-4 study did not state the weight of the population (only BMI) which is important as the dose of standard of care (SoC) in Denmark is depending on the weight. [1] Instead, a Swedish study investigating major FXa related bleedings was used for data on weight as the Swedish population is considered comparable to the Danish. In the Swedish study the mean weight for the population is 75 kg. [4]

Baseline characteristics for the patients included in the analysis are illustrated in table 1 below.

Table 1. Baseline characteristics

Characteristics of patients at baseline	
Mean age of whole cohort	77 years
Percentage of cohort that is female	47 %
Mean weight	75 kg

2.2. Comparator

The comparator in this health economic analysis is prothrombin complex concentrate (PCC) as stated in the protocol by the DMC. [3] In this health economic analysis PCC will be referred to as SoC. The therapeutic indication for PCC is according to EMA treatment of bleeding and as perioperative prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors when rapid correction of the deficiency is required. The administration of human prothrombin complex provides an increase in plasma levels of the vitamin K dependent coagulation factors and can temporarily correct the coagulation defect of patients with deficiency of one or several of these factors. [5]

According to Danish clinical guidelines the dose given is based on the patient's weight. [6]

3. Problem statement

The aim of the health economic analysis is to estimate the incremental costs per patient and the budget impact for the regions if implementing andexanet alfa as standard treatment in Danish hospitals.

4. The health economic model

A decision tree and a Markov model were developed in Microsoft Excel® to capture the costs of andexanet alfa compared with SoC (figure 1 and 2). In the following section all inputs are stated adjusted to fit the 30-day time horizon/cycle length.

4.1. Description of the health economic models

Both a decision tree and a Markov model were chosen to demonstrate the difference in costs for patients treated with andexanet alfa compared to SoC. The rationale behind this decision is to capture the differences in acute clinical costs but also the impact the treatments will have on the costs of long-term late complications which patients risk getting from acute major bleedings.

All patients entering the analysis will experience an acute major bleeding and the decision tree will therefore capture all bleeding events and treatment related costs. It is not assumed that andexanet alfa will affect the frequency of bleedings, only the outcome/time to haemostasis. It is therefore assumed that all patients only have one type of acute major bleeding which only occurs once in this health economic analysis. If patients have more than one type of bleeding occurring at the same time, the highest DRG tariff would be applied for both treatment options and it will not impact the difference in costs between treatments.

Patients surviving in the decision tree will enter the Markov model which only captures the differences in long-term costs due to late complications related to acute major bleeds.

In the analysis, it was not always possible to use probabilities directly from a source as some did not match the 30-day time horizon. In these cases, the formulas below were used to convert inputs to a 30-day probability, where p is the probability, r defined the rate and t denotes the time [7]:

$$r = -\frac{1}{t}\ln(1-p)$$

$$p = 1 - e^{-rt}$$

4.2. The perspective of the analysis

The health economic analysis has a restricted societal perspective and consist of a decision tree of 30 days duration and a Markov model with a time horizon of 21 years consisting of cycles with a 30-day duration.

Costs in the decision tree represents the acute treatment and includes treatment costs and hospitalisation, while the Markov model adds costs of late complications related to acute major bleedings. Results from both the decision tree and the Markov model are represented in the results section.

4.3. Decision tree

The decision tree was chosen as it is suited to demonstrate acute care costs for acute conditions. Andexanet alfa and SoC are acute treatments which are used once when reversal of anticoagulation is needed due to an acute life-threatening or uncontrolled bleeding. For an illustration of the decision tree see figure 1.

It is not expected that andexanet alfa will affect the incidence of bleeding but only the clinical outcome. As a result, all patients which enters the decision tree are patients admitted to hospital due to an acute major bleeding.

The types of acute major bleedings, which are relevant in a Danish setting, were identified in two studies and discussed with a Danish clinical expert before it was implemented in the model. [1] [8] [9] Therefore, patients entering the model had one of the following types of acute major bleeds:

- Intracranial haemorrhage (ICH) – bleeding inside the skull
- Severe gastrointestinal (GI) – bleeding originated from the gastrointestinal tract
- Intraspinal bleeding – bleeding within the spinal canal
- Pericardial bleed – bleeding within the pericardial space
- Retroperitoneal bleed – bleeding within the retroperitoneal cavity
- Intraocular bleed – bleeding into the eyeball

All patients entering the model are in need of reversal of direct FXa inhibitor treatment due to an acute major bleeding. Distribution of acute major bleeds are based on the study population in the ANNEXA-4 study which is 64 % ICHs, 26 % GIs and 10 % other types of bleeds. [1] The Danish clinical expert was consulted to verify the types of bleeds on the other bleeds category which originally was identified by a group of UK clinical experts. [8] As it has not been possible to identify relevant literature stating a distribution between those types of bleedings, it was assumed that these types of bleedings were equally distributed = 2,5 % each. Possible consequences of this is addressed later in the discussion.

All major bleeds were treated with andexanet alfa or SoC and depending on the treatment a probability of surviving or dying was applied in the decision tree. [redacted] For all probabilities used in the decision tree see table 2 and 3.

The time horizon of the decision tree is, as mentioned, 30 days. All acute treatment related events were assumed to be captured within the 30 days. The acute treatment related events included in the decision tree is difference in treatment (cost of medicine), length of stay (days of admissions and patient costs) and probability of surviving. Studies used for probabilities which investigated clinical outcomes of acute major bleeds also used a 30 day follow up period. [1] [9] For an illustration of the decision tree see figure 1.

Figure 1. The 30-day decision tree used for all bleedings.

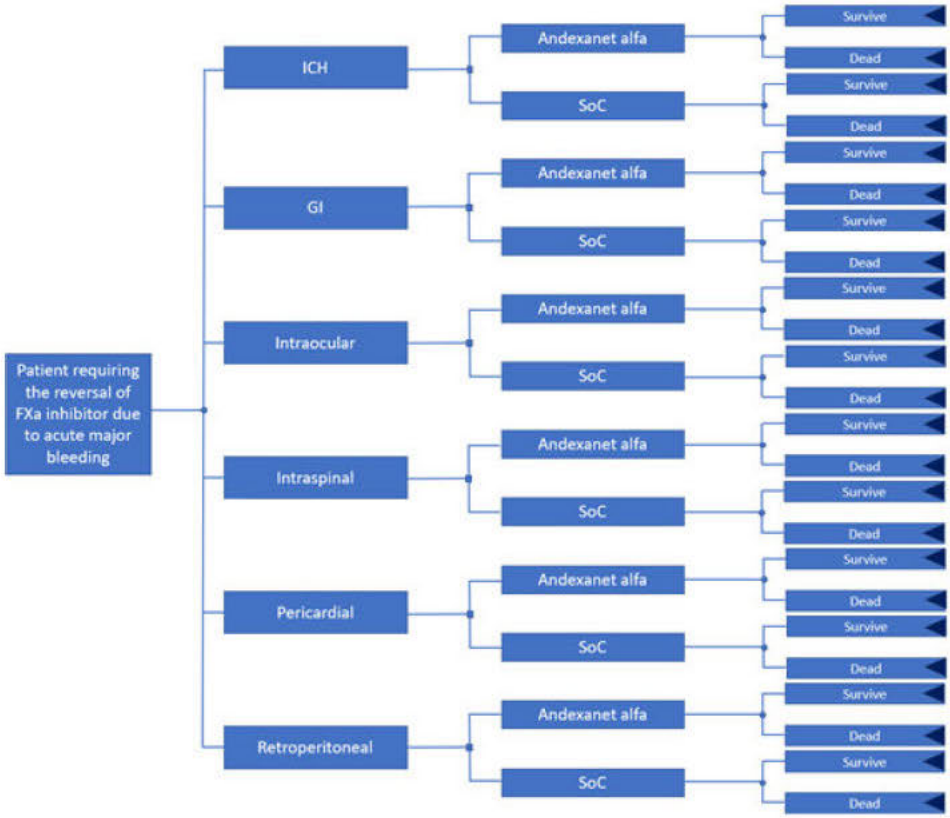
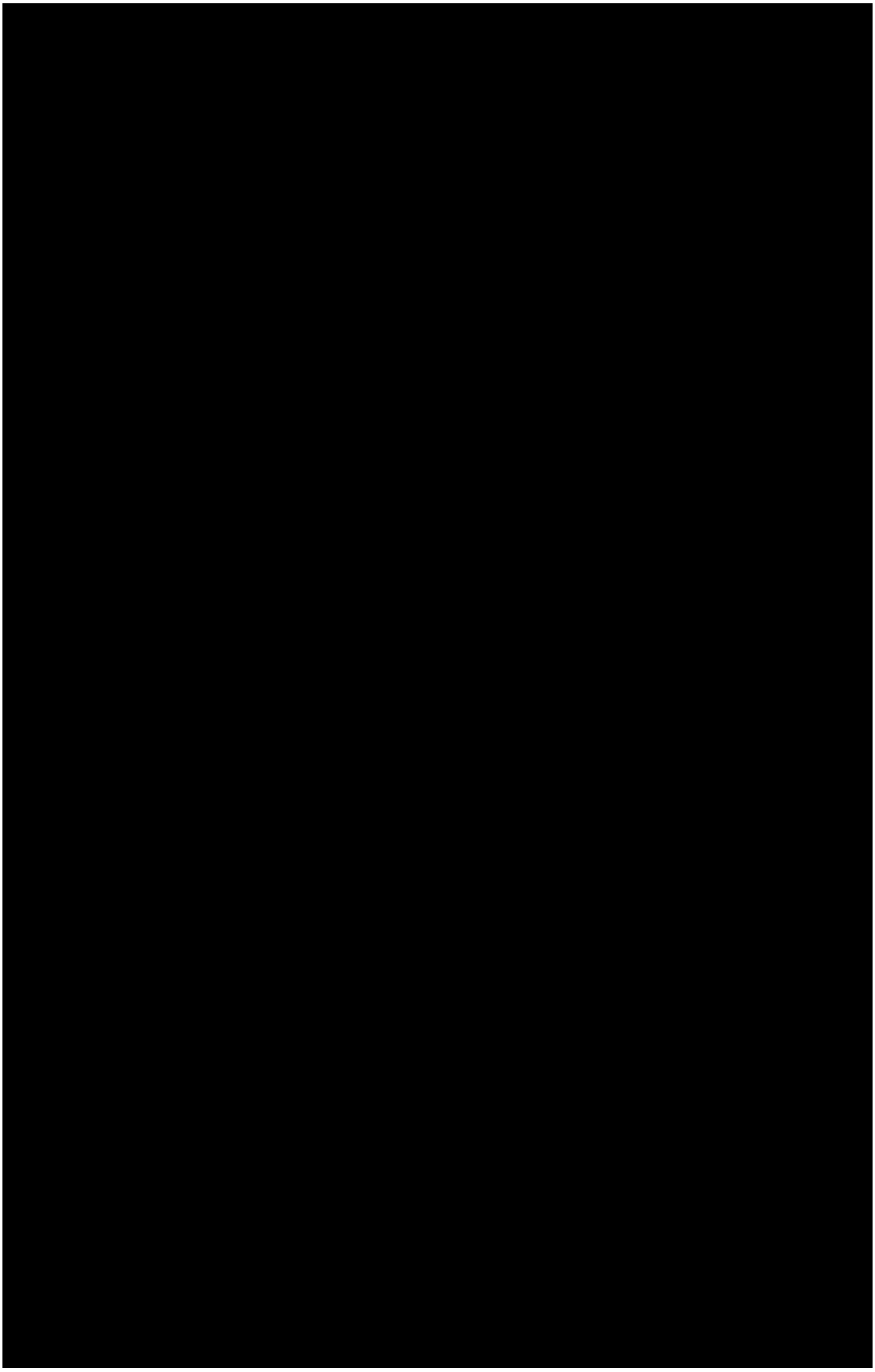


Table 2. Probabilities in the 30-day decision tree for distribution of types of bleedings.

Distribution of bleeding types in the decision tree	Probabilities	References
ICH	0,64	ANNEXA-4 study [1]
[redacted]		

For elaboration on the inputs see section 4.3.

Table 3. Overview of probabilities in the 30-day decision tree



For elaboration on the inputs see section 4.3.

4.4. Markov model

Patients surviving after the 30 days in the decision tree enters a Markov model which demonstrates the differences in long-term costs due to late complications, see Markov model illustration in figure 2. [redacted] Late complications are therefore expected to be different between andexanet alfa and SoC as it is expected that andexanet alfa will stop bleedings more efficiently than SoC for patients treated with FXa inhibitors as andexanet alfa is the only FXa specific antidote. It was identified in published studies that intraocular bleeds and ICH can lead to late complications as blindness and brain injury. [10] [11]

It has been difficult to find directly comparable studies to compare SoC to andexanet alfa since effective haemostasis should be measured in accordance with the International Society on Thrombosis and Haemostasis (ISTH) new standardization criteria [3] and since studies should be comparable. However, in most of the studies on SoC the new standardization criterion has not been used and the time to measure was often longer than in the ANNEXA-4 study (12 hours in ANNEXA-4 study [1] and 24-48 hours in the PCC studies [12] [13] [14] [15])

The ANNEXA-4 study showed that clinical haemostasis was adjudicated as excellent or good in 82 % of patients 12 hours after andexanet alfa infusion. [6] The PCC studies identified to be most comparable to the ANNEXA-4 study, and which also used ISTH, showed an effectiveness of 68 % and 72 % after 24 hours. [14] [12] As this was after 24 hours and not 12 hours like with andexanet alfa it can be assumed that the difference was even bigger than 68 % and 72 % vs. 82 %. [redacted] As a result, a more conservative estimate was used of 20 % in this model. This means that patients treated with andexanet alfa will have 20 % less risk of late complications compared to SoC in the Markov model. The probability of suffering from brain injury as a late complication due to an ICH bleeding was 61 % vs. 48 % for SoC vs. andexanet alfa. The 61 % is based on a literature review by Al-Mufti et al. that states that *"ICH is a potentially devastating neurologic emergency with long-term functional independence achieved in only 12–39 % of cases"* and *"Currently, studies show that <40 % of patients regain functional independence after ICH"*. As a result, a conservative estimate of 39 % was used which means that 61% will risk having late complications (neurological damage) after an ICH. [16] The probability of losing vision in the model from intraocular bleeding was 0,14 % vs. 0,11 % for SoC vs. andexanet alfa. [17]

A lifetime horizon of 21 years was used in the Markov model, and the length of each cycle was 30 days. In the Markov model, patients will either remain in the bleeding survival state or move to the dead state, which is an absorbing state.

The risk of dying after surviving a bleed was based on a study investigating Danes with atrial fibrillation and history of hospitalization from an acute bleeding which resulted in a mortality of 2,2 %. A Danish population suffering from atrial fibrillation was considered appropriate in this setting as these patients often receive anticoagulant treatment. [18] This was confirmed in the ANNEXA-4 safety population as 80 % of the study population were on anticoagulants due to atrial fibrillation. [1] This risk of dying is considered more representative than the general Danish background mortality as the patients are all treated with a FXa inhibitor and are therefore assumed to have a lower health level than the general population. The same mortality was used for both patients treated with andexanet alfa and SoC. The mortality was adjusted based on the general mortality from data from Statistics Denmark to make sure that this population would not outlive the general Danish population. For an overview of probabilities in the Markov model see table 4.

Additionally, a half cycle correction was applied to costs in the Markov model to align with conventional standards.

Figure 2. The Markov model used to demonstrate long term costs for all bleedings.

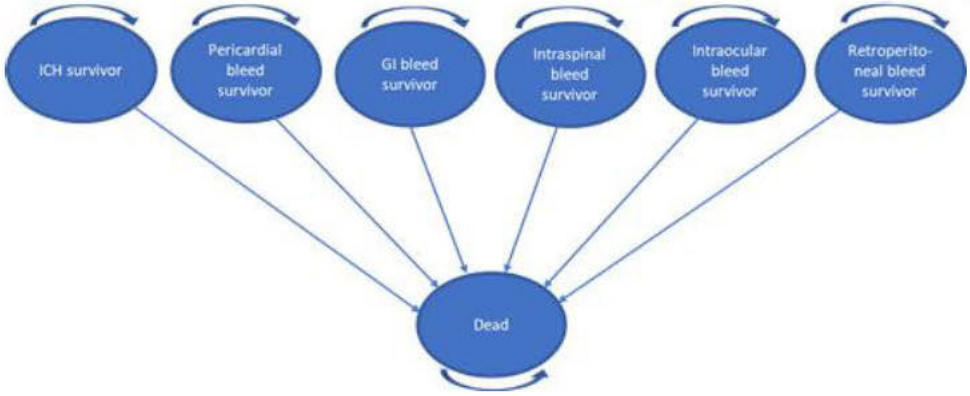


Table 4 Overview of probabilities in the Markov model

Probability for late complications	Probabilities	References
Risk of late complications of an ICH on SoC	0,61	[16] – see assumption in section 4.4.
[redacted]		
Risk of late complications of an intraocular bleed on SoC	0,0014	[17] – see section 4.4.
[redacted]		
Risk of late complications of retroperitoneal, intraspinal and pericardial bleeds	NA	No data available – see section 4.4.
Risk of dying after surviving 30 days	0,022	[19] – see section 4.4.

5. Costs

Costs that were identifiable and considered relevant for andexanet alfa and SoC are included in the model. Costs were considered relevant if they are expected to differ between the two treatments. Costs which fall within the first year are not discounted, while costs after the first year are applied a discount rate of 4 % as defined by the Ministry of Finance and as stated in guidelines from the DMC. [20] [21]

As some of the costs are based on amounts from a previous year, these are adjusted to 2020-prices. This is done by a yearly projection factor based on data from Local Government Denmark (KL) [22], as the adjusted costs are on municipal level, with the use of the following formula:

$$K_n = K_0(1+p)^n$$

Using the yearly projection factor from KL is considered the most representative, as it is only used for municipal costs. Price adjusting can also be done with the use of net price index from Statistic Denmark. However, difference between the two methods is not considered decisive in this analysis as differences in adjusted costs are minor. As an example, price adjustment of one input gave a difference of approximately 250 DKK (3148 DKK vs. 2889 DKK monthly cost of brain injury).

In the following the inclusion and exclusion of costs in the health economic analysis are described which includes relevant treatment costs, hospital costs (including costs for complications and adverse events), costs for the municipality, including rehabilitation, and patient costs.

5.1. Treatment costs

Treatment costs for andexanet alfa and SoC is described in the following section.

5.1.1 Andexanet alfa

Andexanet alfa can be given in a low or high dose depending on the dose of the FXa inhibitor the patient is taking at the time of anticoagulation reversal, and the time since the last dose of the FXa inhibitor. [2]

In the ANNEXA-4 study 16 % of patients received the high dose, while the remaining 84 % received the low dose. As inputs in the model, including risks of surviving or dying, to a high extent are based on the ANNEXA-4 study, the distribution of high and low dose in the ANNEXA-4 study is the one used in the base case analysis. [1] As mentioned previously, the patient population is considered representative for the Danish setting, why this distribution of doses is also considered representative for patients in Denmark.

However, the DMC has stated in their protocol that the expert committee estimates that over 50 % of the patients will receive the high dose. [3] In order to also reflect the assumption in the protocol, there has been made a sensitivity analysis with 50 % of patients on high dose and 50 % of patients on low dose.

Andexanet alfa is sold in packages of four vials, which each contains 200 IU. The pharmacy purchase price (AIP) excl. VAT for a package of andexanet alfa is 95.000 DKK resulting in a price per vial of 23.750 DKK. [23] Waste of opened vials are included in the costs, since sharing of opened vials is not expected. Unused vials from opened packages are not included in the costs.

The low dose of andexanet alfa is 880 IU, which means that five vials are used for the low dosage. Therefore, the costs for a treatment with low dose is 5 x 23.750 DKK = 118.750 DKK. The high dose is 1760 IU, which means that nine vials must be used. This results in a price of 9 x 23.750 DKK = 213.750 DKK for the high dose. If 16 % receives high dose and 84 % receives low dose, the average drug cost for a patient is 133.950 DKK. Additionally, if 50 % of the patient population receives high dose and 50 % receives low dose this will result in an average cost of 166.250 DKK, which will be used in a sensitivity analysis.

As a result, there will be a waste of 120 IU with the low dose and of 40 IU with the high dose, which is included in the analysis.

5.1.2 SoC

Guidelines from the Danish Society of Cardiology states that PCC must be given in a weight dependent dose. According to the guidelines, the recommended dose of PCC is 25 IU/kg. [18] In this analysis, the average patient weights 75 kgs resulting in a dose of 1875 IU PCC.

The pharmacy purchase price (AIP) excl. VAT for PCC in sizes of 1000 IU is 4860,00 DKK. [23] As two packages of 1000 IU is needed in order to give the dose of 1875 IU, the total cost for the average patient is 9.720 DKK.

There will be a waste of 125 IU, which is included in the analysis as sharing of opened doses of SoC is not expected.

5.2. Hospital costs

As all patients in the analysis are admitted to the hospital, this is included in the analysis. As the patients on andexanet alfa and SoC are equally admitted with the same distribution of bleedings, there is not applied a DRG tariff for this, as it is not expected to differ between the groups. However, it was assumed in the analysis that patients treated with SoC will be admitted for a longer time period. The mean patient treated will SoC are assumed to be admitted for 10,72 days, which is based on the Orange study and calculated as the weighted average between patients discharged and still inpatient.

Table 5 Overview of days of admission in the Orange study

Variable	Number
Patients dying in hospital	446

Patients discharged from hospital	1.413
Still inpatient after 30 days	273
Lost to follow up	60
Total	2132
Days in hospital for discharged patients	7
Days in hospital before death	3
Weighted average days in hospital	10,72

All inputs in table 5 above are from the Orange study. The 10,72 was calculated as: (1413/(1413+273))*7+(273/(1413+273))*30= 10,72. [9]

It has not been possible to identify published data for length of stay for patients treated with andexanet alfa after a bleeding. However, as andexanet alfa is expected to stop bleedings more efficiently than SoC, it is assumed that these patients will have fewer bed days at the hospital. [redacted] As mentioned previously, the clinical haemostasis of andexanet alfa was in a study adjudicated as excellent or good in 82 % of patients 12 hours after infusion compared to 68 % and 72 % after 24 hours in the PCC studies identified to be most comparable. [1] [12] [14] As the time horizon in the studies differed, it is assumed that the difference was even higher if the same time horizon has been used. As a consequence, it is assumed that the length of stay is reduced by 20 % when treating with andexanet alfa due to the more efficiently stopping of the bleeding.

Length of stay is an uncertain estimate due to studies only reporting the median length of stay and furthermore, there has not been published studies yet demonstrating the difference between the two treatments in this analysis. As a result, a sensitivity analysis has been made with no difference in length of stay.

The difference in costs for length of stay is based on cost for an extra bed day above the trim point. This cost is based on the DRG tariff DK 'DRG 2020 Langliggertakst' [24], and is used as it illustrates the difference in costs regarding bed days for SoC versus andexanet alfa. The DRG tariff applied is 2.127 DKK per extra bed day.

5.3. Costs for complications and adverse reactions

Complications and adverse reactions occurring from the two treatments during hospitalization has not been included since it has not been possible to document the differences regarding this for andexanet alfa and SoC in comparable studies. The adverse reaction profile among PCC studies are heterogenous and it was not possible to base calculations on a comparative study as no study exists which compares the two treatments. Additionally, it is assumed that differences in short term adverse reactions and complications

would be captured within the DRG tariffs in both treatments and will not make a difference in costs.

Thromboembolic events are an adverse reaction/complication of high importance and interest in this patient population which has also been highlighted in the protocol. [3] But as no comparable studies reporting thromboembolic events of andexanet alfa and PCC could be identified, a possible difference could not be quantified and analysed and therefore it was assumed that there is no difference in costs due to thromboembolic events. This may either under- or overestimate the total incremental cost if there is a true difference between treatments. For studies identified see table 6 below.

As mentioned above, it has not been possible to draw conclusions regarding costs for either complications or adverse reactions as outcomes were measured within different time frames and using different definitions and methods. Review of studies identified are listed in the table below.

Table 6 Overview of the different adverse reactions identified in studies from the search string provided by the DMC are shown in the table below

Treatment	Studies included in the analysis	Treatment	Review
Andexanet alfa	Connolly et al. (2016) [25]	Andexanet alfa	No infusion reactions; no antibodies to FXa or FX; no neutralizing antibodies to andexanet alfa; TEs in 12 patients (18%) with some patients having more than one event; 10 deaths (15%); 18 patients (27%) restarted anticoagulation within 30 days
	Connolly et al. (2019) [1]	Andexanet alfa	34 (10%) of patients had a TE during the 30-day follow-up (7 MI, 14 ischemic strokes, 1 TIA, 13 DVT 5 PE); 2 infusion reactions (non-severe); ion
	Stevens et al. (2019) [26]	Andexanet alfa (15% on high dose, 85% on low)	4 (31%) patients experienced 5 TEs within 30 days after treatment (the median time to event was 6.5 days [IQR: 1-26 days]) including DVT, ischemic stroke, PE, MI, and superficial venous thrombosis (2/4 patients who had a TE were also treated with FVIIa and/or 4F-PCC); 8 patients were not restarted on anticoagulation during their hospital admission; the median time to initiation of anticoagulation (among those patients who were restarted) after bleed was 4.5 days (IQR: 2-5.5 days); 2 (15%) of patients died within 30 days after treatment (median time to event was 2 days [range: 1.5-2.5]), both patients had an ICH with a Glasgow Coma Score (GCS) of 8 and 4, respectively. No patients in the non-ICH group died
	Allison et al. (2018) [27]	PCC 35 U/kg	No TEs reported were attributable to 4F-PCC; however, no routine imaging studies were done unless clinically indicated. 5/33 died (care was withdrawn in 3, 1 died from pneumonia and 1 from multi-organ failure)
PCC	Arachchillage et al. (2019) [28]	PCC 16,7-50 U/kg (rivaroxaban; mean 26,8) and 18,5-43 U/kg	Recurrent bleeding within 48h was 17,5% and 27,5% for patients on rivaroxaban and apixaban, respectively (20% and 15% in ICH patients; recurrent ICH bleeding was 12% and 9,5%); recurrent bleeding within 30 days was 20% and 30,8% for riva-

		(apixaban; mean 25)	roxaban and apixaban, respectively; anticoagulation was re-started in 25% and 32,5% patients on rivaroxaban and apixaban, respectively (16% and 19% in ICH patients)
	Berger et al. (2019) [29]	PCC 25 U/kg	One patient developed an ischemic stroke 0.5 days after 4F-PCC; the second patient developed a left lower extremity DVT 7.3 days after 4F-PCC. Among patients who died, 2 were transitioned to withdrawal of care, and the other 2 experienced a cardiac arrest.
	Dybdahl et al. (2019) [30]	PCC recommended dose was 50 U/kg	The no reversal group had a significantly higher incidence of ischemic stroke or TIA than the 4F-PCC group (4F-PCC: 0%; no reversal: 14.8%). There was no difference in the incidence of VTE or MI between the two groups. After controlling for ISS, there was no significant difference in mortality, ICU length of stay, or ischemic stroke or TIA.
	Frontera et al. (2020) [12]	PCC recommended dose was 50 U/kg	TEs consisted of one patient with acute ischemic stroke and one with DVT. 50% of patients had a good discharge disposition and the overall median length of stay was 5 days
	Grandhi et al. (2015) [31]	PCC median dose 3177 IU (2124-4770)	The overall in-hospital mortality rate was 33%; families withdrew care on 4 patients, and 2 patients on apixaban expired due to respiratory failure secondary to aspiration pneumonia with no evidence of haemorrhage progression on head CT
	Harrison et al. (2018) [32]	PCC recommended dose was 50 U/kg	Mortality and outcome data and lack of VTE complications suggest that 4F-PCC is unlikely to worsen outcomes with factor Xa inhibitor–associated ICH but the findings suggest no clear evidence of benefit or harm with 4F-PCC for patients with factor Xa inhibitor–associated ICH.
	Majeed et al. (2017) [33]	PCC median dose 2000 IU (1500-2000) Apixaban 26.7 U/kg (22.0-29.9) Rivaroxaban 26.7 U/kg (20.8-29.4)	The only adverse events reported are TEs. 1 ICH patient on apixaban died from stroke and 1 ICH patient on rivaroxaban died from suspected PE 18 days after treatment. Among 27 deaths within 30 days, the cause of death was due to the direct effect of the bleeding in 66.7% of patients, sepsis and multiorgan failure In 25.9%, and cardiac arrhythmia and arrest in 1 patient each (3.7%).
	Schenk et al. (2018) [34]	PCC 25 U/kg	3 died (septic shock (1), progressive cancer (1) and ICH (1)). All deaths were considered to be unrelated to the study medication; 3/13 patients showed signs of re-bleeding (progressive ICH) after administration of PCC; other serious adverse events were an epileptic event, ischemia caused by thromboembolic closure of the femoral artery bifurcation, sepsis and embolic arteria cerebri anterior infarct (one patient).
	Schulman et al. (2018) [14]	PCC 2000 IU	6 TEs were diagnosed 1, 2, 9, 12 and 22 (2) days after PCC; 9 (14%) patients died whereof 8 had ICH (22% of the intracranial bleeds), 7 of the deaths were adjudicated as 'a result of the index (intracranial) bleeding event'. 1 death was in a patient with self-inflicted stab wounds to the chest. There were 8 additional serious adverse events, all among patients with initial ICH; 6 with prolonged hospitalization due to extracranial bleeding (GI 1; gross haematuria—2), and 1 patient each with cellulitis, infection + hypernatremia + delirium, neurological

			deterioration due to expansion of previously evacuated subdural haematoma; and two with re-hospitalizations for gastrointestinal bleeding)
	Sheikh-Taha (2019) [35]	PCC 50 U/kg	8 (27.6%) failed to achieve haemostasis, all of them suffered from ICH (6 died during hospitalization and 2 suffered from neurologic deterioration upon hospital discharge).
	Sin et al. (2016) [13]	PCC recommended dose was 25 U/kg	The single patient treated with FXa inhibitor that experienced a TE was treated pre surgery; no other safety parameters presented separately for FXa inhibitor patients
	Tao et al. (2018) [15]	PCC mainly 25-50 U/kg	3 patients continued to bleed after treatment with 4F-PCC, whereof 2 died from haemorrhage; 1 TE (upper extremity DVT) occurred in a patient on rivaroxaban who had ICH (1 day after treatment with PCC)
	Tellor et al. (2018) [36]	PCC 50 U/kg, 25 U/kg or 10 U/kg; recommended was 50	1 person had a DVT; 6 people died (2 indicated for emergency surgery, 3 for ICH and 1 for intraperitoneal bleed). 3 deaths were not directly attributable to bleeding complications. 24/29 did not continue DOAC therapy at discharge

5.4. Municipal costs

A description of the rehabilitation costs in the municipality is made in the following section. Additionally, there is a description of costs that are not included and why these are omitted from the analysis.

5.4.1. Rehabilitation costs

It is assumed that some of the patients in the model, who have suffered from either an ICH or an intraocular bleed, will develop late complications which is expected to result in rehabilitation costs.

Rehabilitation at hospitals has not been included in studies identified for andexanet alfa and SoC. Therefore, it has not been possible to identify any differences in costs, and as a consequence these are not included in the analysis.

However, long-term rehabilitation costs in the municipality have been included for ICH and intraocular bleeds as these have known complications from acute major bleeds. [10] [11] [redacted]

The National Board of Social Services has in a report estimated the costs for patients, who have been hospitalized due to an acute event, for instance apoplexies, resulting in a brain injury. In this report, it is estimated that the costs for the municipality, including rehabilitation and home care, for the first two years are approximately 60.000 DKK. [37] This is divided on a monthly basis and adjusted to a 2020 price level according to the methods described in the beginning of section 5. The monthly (30-day cycle) cost for rehabilitation due to an ICH is estimated to 3.148 DKK.

Data for cost of blindness in Denmark was limited and as a result a Danish health economic analysis from DSI (Institut for Sundhedsvæsen) investigating the cost of diabetes related eye disease and blindness was used. [38] Again, this cost has been divided to a monthly cost and adjusted to a 2020-price level. The monthly costs for blindness because of an intraocular bleeding are estimated to 3.983 DKK.

As it has not been possible to find any representative published data regarding late complications of retroperitoneal, intraspinal and pericardial bleeds, costs for rehabilitation for these bleeding types are not included in the model.

5.5. Patient costs

As all patients entering the model on both SoC and andexanet alfa are admitted with a bleeding, patient time for transportation is therefore not included in the model as it will not differ between the two groups and therefore not affect the outcome. Patient time used on the difference in hospital stay are included and calculated with the use of the unit cost based on the average hourly wage in Denmark after tax which is 179 DKK per hour. [39] As stated earlier, patients treated with andexanet alfa is assumed to be admitted for 20 % less time than SoC. As a result, the difference in patient costs was calculated as 179 DKK*24 hours*2,144 days = 9.210 DKK extra for patients treated with SoC and surviving in the decision tree. No patient costs were added to andexanet alfa.

Patients, who suffers from late complications due to a bleeding, is expected to have increased use in patient time on health care resources, such as visits to general practitioner or home care. However, it has not been possible to document this resource use – neither on SoC or andexanet alfa – why costs for this are not applied in the model. It is also expected that the patients, who still are in the work force, risk to have lower availability on the job market, but this is also not included due to the lack of documentation and the limited societal perspective in the model. However, due to the high mean age of the population, it is expected to be for a minimum of patients.

6. Sensitivity analysis

Three sensitivity analyses have been made in order to illustrate consequences of changes in the parameters which are expected to be the most uncertain ones. There has been made several sensitivity analyses, on different parameters. [redacted]

6.1. Changed distribution of doses of andexanet alfa

Andexanet alfa can, as mentioned, be administrated in either low or high dose. As the DMC in their protocol estimated another distribution between the proportion of patients on either the low or high dose compared to the ANNEXA-4 study, which is used in the base case, the different dosing regimen is illustrated in the sensitivity analysis.

The DMC has stated in their protocol that the expert committee estimates that a minimum of 50 % of the patients will receive the high dose. As a result, a base case analysis for 50 % of patients on high dose and 50 % of patients on low dose has been made. The average cost if 50 % of the patient population receives high dose and 50 % receives low dose is 166.250 DKK. It is possible to change the input in the Excel sheet by a dropdown-menu (highlighted in green) in the cost inputs-sheet in cell I13.

6.2. No difference in length of stay

It is assumed that there will be a reduced length of stay after treatment with andexanet alfa based on studies, which showed that andexanet alfa is more efficient when it comes to stopping the bleedings than SoC and [redacted] In the base case analysis, a reduction of length of stay of 20 % with andexanet alfa-treatment has been used.

However, as there are some uncertainties regarding this estimate, it has been chosen to make a sensitivity analysis, where no difference in length of stay is used in the analysis. It is possible to change this input in the results sheet, where a drop-down menu (highlighted in green) can be found in cell D8.

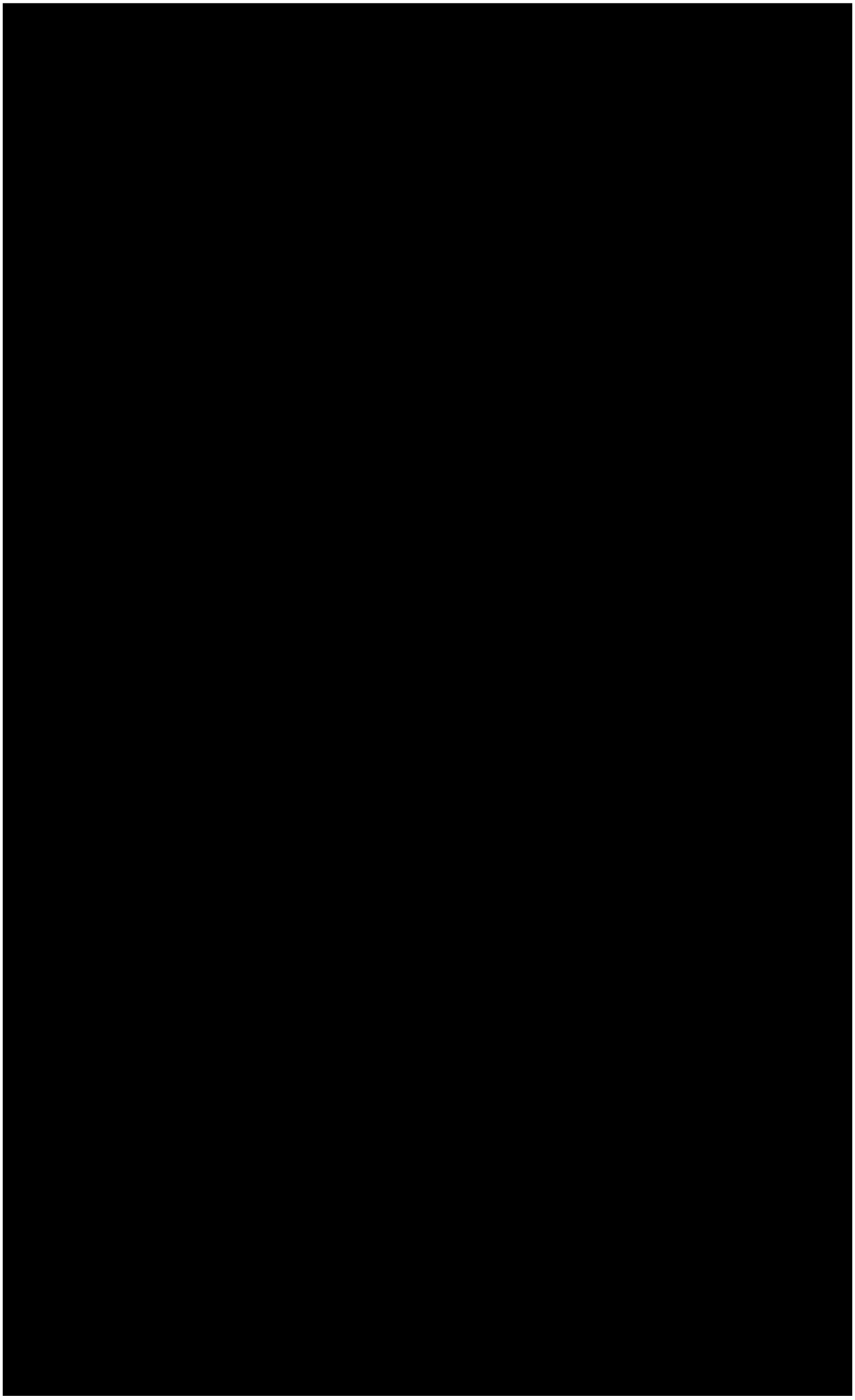
6.3. Changed reduction in late complications

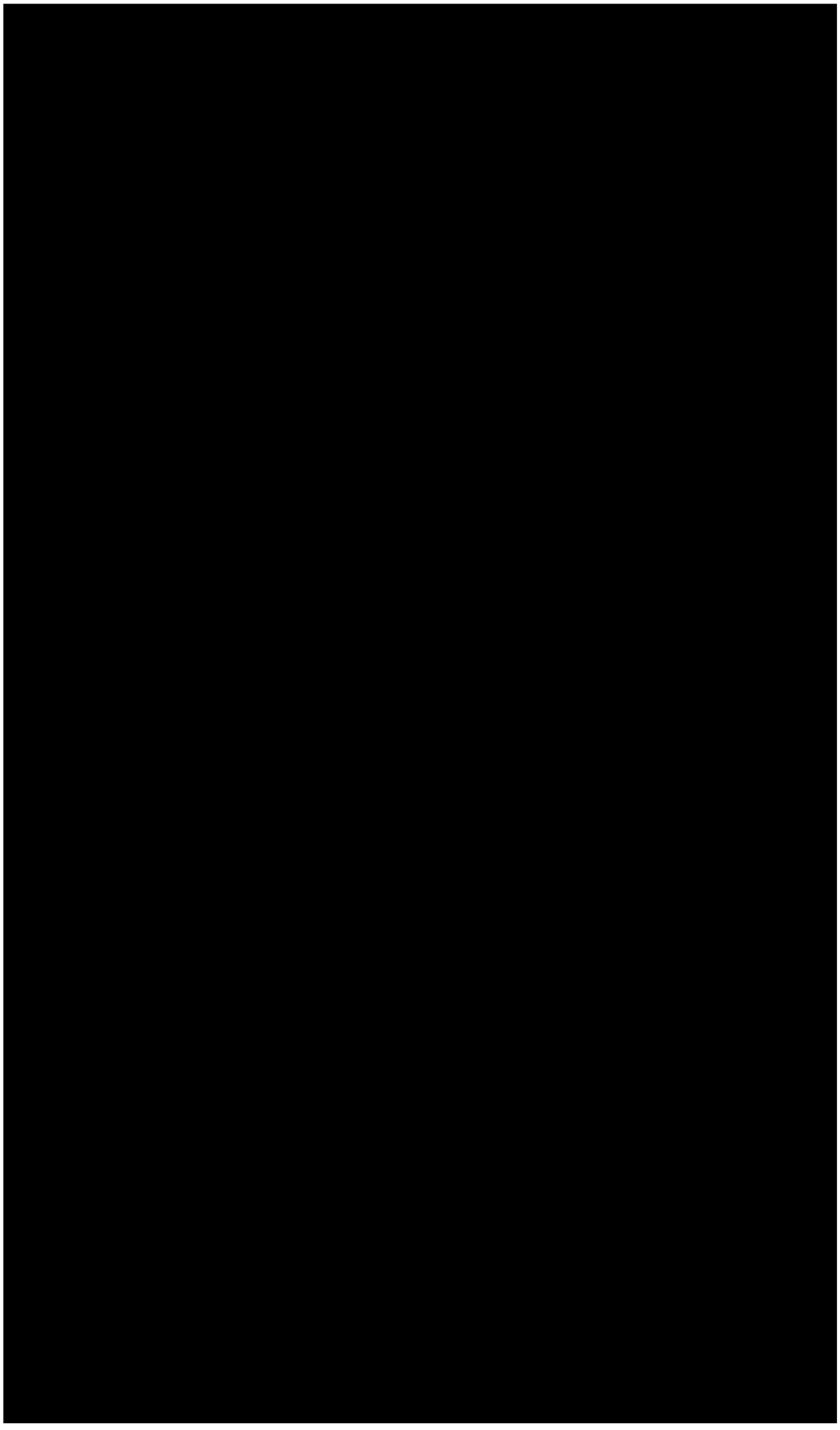
In the base case analysis, a 20 % reduction in late complications for andexanet alfa compared to SoC is applied for both ICH and intraocular bleed. As there is some uncertainty regarding the estimate of reduction in late complication, as it is based on clinical opinion, a sensitivity analysis has been made to investigate potential changes in the reduction.

As ICH is more common and patients more often experience long-term consequences due to ICH, this is the long-term consequence, which drives most costs in the long-term perspective of the analysis. Therefore, it is analysed how changes in the assumption in the reduction of complications influence the results. For ICH, there has been applied a changed reduction of 0 %, 10 % and 30 % to analyse the impact on the results.

Only a limited patient population experience intraocular bleeding, and of those only a very limited part suffers from long term consequences due to the intraocular bleeding. Due to this, it has been investigated how a changed assumption to 0 % reduction will influence the results.

The inputs can be changed in the results sheet, where a drop-down menu (highlighted in green) can be found in cell D10 and D11.





7. Basic assumptions

Table 9. List of basic assumptions in this health economic analysis

Basic assumptions	
Treatment	Andexanet alfa
Comparator	Prothrombin complex concentrate (PCC)
Time horizon	30-day decision tree and 21 years Markov model
Discounting	4 %
Costs included	Treatment costs, hospital costs, municipal costs, patient costs
Dose	Andexanet alfa: • Base case: 16 % high dose and 84 % low dose • Sensitivity analysis: 50 % high dose and 50 % low dose PCC: 25 IU/kg
Inclusion of waste	Yes
Treatment length	Only one treatment per bleeding
Analysis perspective	Restricted societal perspective
Methods for evaluating uncertainties	Relevant sensitivity analyses

8. Results

8.1. Results from decision tree

For the decision tree with a time horizon of 30 days the total costs without patient costs for andexanet alfa is 133.950 DKK and for SoC 12.518 DKK resulting in an incremental cost of 121.432 DKK. For the decision tree with a time horizon of 30 days the total costs with patient costs for andexanet alfa is 133.950 DKK and for SoC 18.170 DKK resulting in an incremental cost of 115.780 DKK.

The costs can be divided into medicine costs, hospital costs and patient costs as these are the ones applied in the decision tree. A table overview of the costs for the decision tree divided into these components can be found in table 10 below.

Table 10. Costs components and total costs for each treatment option.

Cost components	Andexanet alfa (DKK)	SoC (DKK)	Incremental costs (DKK)
Medicine costs	133.950	9.720	-
Hospital costs	0	2.798	-
Patient cost	0	5.652	-
Total with patient costs	**133.950**	**18.170**	**115.780**
Total without patient costs	**133.950**	**12.518**	**121.432**

8.2. Results from Markov model

In the Markov model total cost without patient costs for andexanet alfa is 176.676 DKK and for SoC 45.101 DKK resulting in an incremental cost of 131.575 DKK. In the Markov model total cost with patient costs for andexanet alfa is 176.676 DKK and for SoC 50.753 DKK resulting in an incremental cost of 125.923 DKK.

Cost components and total costs for the life-time horizon are divided into medicine costs, hospital cost, societal costs, and patient costs in table 11 below. Societal costs are defined as costs occurring outside hospital.

Table 11. Costs components and total costs for each treatment option.

Cost components	Andexanet alfa (DKK)	SoC (DKK)	Incremental costs (DKK)
Medicine cost	133.950	9.720	124.230
Hospital cost	-	2.798	-2.798
Societal cost	42.726	32.583	10.142
Patient cost	0	5.652	-5.652

Total with patient cost	**176.676**	**50.753**	**125.923**
Total without patient cost	**176.676**	**45.101**	**131.575**

8.3. Sensitivity analyses

8.3.1. Changed distribution of doses of andexanet alfa

Since andexanet alfa can be given in a high and low dose there can be differences regarding what dosage should be used. As the DMC stated in their protocol that they assume that minimum half of the population will get high dose, this is reflected in the sensitivity analysis, where 50 % receives low dose and 50 % receives high dose. [3]

The sensitivity analysis with a life-time horizon resulted in a total cost including patient costs for patients treated with andexanet alfa of 208.976 DKK and 50.753 DKK for SoC resulting in an incremental cost of 158.223 DKK per patient, see table 12 below.

The sensitivity analysis resulted in a total cost excluding patient costs for patients treated with andexanet alfa of 208.976 DKK and 45.101 DKK for SoC resulting in an incremental cost of 163.875 DKK per patient, see table 12 below.

Table 12. Total costs and incremental cost with 50/50 receiving high or low dose.

	Total costs (DKK)
Standard of care without patient costs	45.101
Standard of care with patient costs	50.753
Andexanet alfa*	208.976
Incremental cost without patient costs	163.875
Incremental cost with patient costs	158.223

**As earlier stated, no patient cost has been added to andexanet alfa.*

8.3.2. No difference in length of stay

As there are some uncertainties regarding length of stay, there has been made a sensitivity analysis in which it is assumed that there is no difference in length of stay and therefore no difference in costs for hospitalisation. In this sensitivity analysis the costs are therefore for the medicine and for the difference in long term late complications.

The sensitivity analysis with no difference in length of stay resulted in a total cost with a life time horizon for patients treated with andexanet alfa of 176.676 DKK and 42.303 DKK for SoC resulting in an incremental cost of 134.373 DKK per patient, see table 13 below.

This is the same with and without patient costs as patient cost are applied for the extra bed days, which in this sensitivity analysis is equal.

Table 13. Total costs and incremental cost with no difference in length of stay between patients treated with andexanet alfa and SoC

	Total costs (DKK)
Standard of Care	42.303
Andexanet alfa	176.676
Incremental cost	134.373

8.3.3. Changed reduction in late complications

To investigate changed reduction in late complications for a life time horizon for ICH and intraocular bleedings for andexanet alfa compared to SoC a sensitivity analysis regarding this was made. As previously described, a reduction in late complication for ICH on 0 %, 10 % and 30 % has been applied. Additionally, a reduction of 0 % of late complications for intraocular blindness has been performed. Results are presented in table 14 below.

Table 14. Incremental costs for patients treated with andexanet alfa compared to SoC with changed reduction in late complications

	Incremental costs with patient costs (DKK)	Incremental costs without patient costs (DKK)
Base case	125.923	131.575
Incremental cost with 0 % reduction in late complications for ICH	137.492	143.144
Incremental cost with 10 % reduction in late complications for ICH	132.064	137.716
Incremental cost with 30 % reduction in late complications for ICH	121.206	126.858
Incremental cost with 0 % reduction	125.925	131.577

in late complications for intraocular bleed		

[redacted]

8.4. Budget impact analysis

The budget impact analysis is based on the assumed speed of market uptake. The first year a market uptake of 5 % was assumed, 10 % the second year, 15 % the third year, 20 % the fourth year and 25 % the fifth year if andexanet alfa is recommended as standard treatment. [redacted]

[redacted]

There is also an uncertainty connected to the size of the patient population. The following is based on a population size stated from the protocol of 160-280 with an average population of 220 patients.

Table 16 below illustrates the number of patients on either andexanet alfa or SoC if a recommendation is given vs. if a recommendation is not given. Costs in this budget impact analysis include pharmaceutical prices and hospital costs (extra bed days), and patient costs are excluded from the budget impact analysis as required by the DMC methods. No costs have been discounted in the budget impact analysis.

Table 16. Number of patients on andexanet alfa or SoC if a recommendation is given vs. if a recommendation is not given.

		Year 1	Year 2	Year 3	Year 4	Year 5
Patient numbers If recommendation is given	Andexanet alfa	11	22	33	44	55
	SoC	209	198	187	176	165
Patient numbers if recommendation is not given	Andexanet alfa	5	5	11	11	11
	SoC	215	215	209	209	209

If andexanet alfa I recommended, it is assumed that the market uptake the first year will be 5 %, 10 % the second year, 15 % the third year, 20 % the fourth year and 25 % the fifth year. This market uptake will for the population size of 220 in total results in the costs below, see table 17.

Table 17. If andexanet alfa is recommended as standard treatment

Year 1	Year 2	Year 3	Year 4	Year 5
1.335.748	2.671.497	4.007.245	5.342.994	6.678.742

If andexanet alfa is not recommended as standard treatment, the market uptake is expected to be both slower and lower [redacted] [8]. In that case, the market uptake is expected to be 2,5 % for the first and second

year and 5 % for the third, fourth year and fifth year. This resulting in the costs in table 15 below.

Table 18. If andexanet alfa is not recommended as standard treatment

Year 1	Year 2	Year 3	Year 4	Year 5
607.158	607.158	1.335.748	1.335.748	1.335.748

The economic consequences if the treatment is recommended versus if it not recommended is found in table 19.

Table 19. Difference in costs with and without a recommendation

Year 1	Year 2	Year 3	Year 4	Year 5
728.590	2.064.338	2.671.497	4.007.245	5.342.994

8.5. Sensitivity analyses for budget impact

Due to possible ranges of population size, a sensitivity analysis has been made for both a population size of 160 and 280 patients, which were the range stated in the protocol by the DMC. [3] It is possible to change this input in cell D8 in the BiM-sheet (highlighted in green).

A population size of 160 patients resulted in the difference illustrated in table 20 below in costs with and without recommendation (market uptake being the same as base case).

Table 20. Difference in costs with and without a recommendation for population size of 160 patients

Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
485.727	1.457.180	1.942.907	2.914.360	3.885.814

A population size of 280 patients resulted in the below difference illustrated in table 21 below in costs with and without recommendation (market uptake being the same as base case).

Table 21. Difference in costs with and without a recommendation for population size of 280 patients

Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
850.022	2.550.065	3.400.087	5.100.130	6.800.174

9. Discussion

The results from the decision tree with a time horizon of 30 days estimate the total costs excluding patient costs for andexanet alfa to be 133.950 DKK per patient and for SoC to be 12.518 DKK per patient resulting in an incremental cost of 121.432 DKK per patient. When including patient costs in the analysis, the costs for andexanet alfa is 133.950 DKK and for SoC 18.170 DKK resulting in an incremental cost of 115.780 DKK.

With a lifetime horizon of 21 years in the Markov model, the total cost excluding patient costs for andexanet alfa was 176.676 DKK per patient and 45.101 DKK per patient for SoC resulting in an incremental cost of 131.575 DKK per patient. When including patient costs in the Markov model, the total cost with patient costs for andexanet alfa is 176.676 DKK and for SoC 50.753 DKK resulting in an incremental cost of 125.923 DKK.

In the base case analysis costs were mainly driven by medicine costs. However, societal costs are higher for andexanet alfa due to a higher probability of surviving from ICHs which is the most frequent type of bleeding.

The sensitivity analysis which reflects the expected distribution of dose stated in the DMC protocol with a 50/50 dosing regimen resulted in a total cost without patient costs with a life-time horizon for patients treated with andexanet alfa of 208.976 DKK and for SoC of 45.101 DKK resulting in an incremental cost of 163.875 DKK per patient. The same sensitivity analysis resulted in costs for andexanet alfa of 208.976 DKK and 50.753 DKK for SoC resulting in an incremental cost of 158.223 DKK per patient when including patient costs.

The second sensitivity analysis regarding LOS confirmed that the result of the base case analysis is robust as the incremental costs did not change much when removing the differences in days of admission as this can be considered an uncertain estimate. Equal length of stay resulted in a total cost with a life-time horizon for patients treated with andexanet alfa of 176.676 DKK and for SoC of 42.303 DKK resulting in an incremental cost of 134.373 DKK per patient, which is very close to the base case results. This is the same with and without patient costs as extra costs due to patient time used on admission is not applied as this sensitivity analysis assumes equal length of stay.

The sensitivity analysis, which investigated the uncertainty regarding the reduction in late complications when treating with andexanet alfa, showed that changes in the assumption only let to minor changes in incremental costs. When changing the reduction in late complications for ICH, the incremental costs ranged from 137.492 DKK with 0 % reduction and to 121.206 with 30 % reduction, when including patient costs. Both results are close to base case at 125.923 DKK. Additionally, when changing the reduction in late complications to 0 %, when treating with andexanet alfa for patients experiencing an intraocular bleeding, the conclusion is the same. In this case the incremental costs are

125.925 DKK, which is almost identical to the base case at 125.923 DKK. Therefore, the last sensitivity analysis illustrates that changes in the reduction of late complications when treating with andexanet alfa only have a very limited impact on the results.

[redacted] but it has not been possible to include neither costs for rehabilitation at the hospital nor costs of rehabilitation in the municipality for all the six different types of bleeds. This is not included as it has not been possible to estimate the costs, including whether there is a difference between andexanet alfa or SoC. However, as andexanet alfa has proved to stop bleedings more efficiently than SoC, it is expected that patients treated with andexanet alfa will have lower resource use regarding both rehabilitation during their hospital stay and rehabilitation in the municipality for a longer period of time. [1] [12] [14] Even though some costs of rehabilitation have been included in the analysis by reducing the days admitted to hospital and the proportion developing late complications for patients treated with andexanet alfa, it is still believed that these costs may be underestimated. As a result, it is expected that the advantages of andexanet alfa is underestimated as andexanet alfa can result in a bigger difference in resource utilization than illustrated in this analysis.

Complications and adverse reactions occurring from the treatment with andexanet alfa or SoC during hospitalization have been excluded from the analysis as it has not been possible to document the differences between the two treatments regarding this in comparable studies. It is assumed that any differences of short-term adverse reactions and complications that might exist in real life will be covered by the DRG tariffs in both treatments resulting in no differences in costs. Additionally, it has not been possible to identify comparable studies reporting thromboembolic events of andexanet alfa and SoC, why costs regarding this are omitted from the analysis. Omitting thromboembolic events can either under- or overestimate the total incremental cost if there is a true difference between treatments.

It has not been possible to include long term patient costs as estimates have not been possible to identify. Nonetheless, due to the higher efficacy of andexanet alfa, it is assumed that patients treated with this will have a better outcome and therefore use e.g. less time on transportation to health services and rehabilitation resulting in spared patient costs. The better outcome for patients treated with andexanet alfa is also expected to influence their quality of life, which is not included in the analysis due to the methods in Denmark but is expected to have an impact in real life.

In this analysis it has not been possible to base the full distribution of bleeds on published studies. It was therefore assumed that the last 10 % of bleeds stated as other bleeds in published literature was equally distributed and types of bleeds identified by a clinical expert. [8] [1] Intraocular bleeding is the only bleeding type among the four which is

associated with costs that differs between the two treatment options. The only difference in cost are long-term cost due to blindness as a long-term consequence from an intraocular bleeding. To address this uncertainty, the impact on the analysis if the distribution of bleeds is changed was investigated by calculating the expected value when changing the distribution. When calculating the expected value, the mortality has not been included as mortality is the same for each treatment option and will not influence the result. The expected value is calculated by multiplying the estimated cost by its probability. The only difference in cost between the four bleeding types are long-term cost due to blindness as a long-term consequence from an intraocular bleeding. In the model only 0,14 % and 0,11 % of patients risk becoming blind after the bleeding which means that the expected value for standard of care a life time horizon can be calculated as 2,5 % * 0,14 %* ((12*3.983 DKK)*21) = 35,1 DKK. If all 10 % of patients had ocular bleeds the expected value would be: 10 % * 0,14 %* ((12*3.983 DKK) *21) = 14.0 DKK). Even though this gives us the expected value, the calculation does not take time and discounting into account. However, taking the acute setting into consideration and the fact that discounting only reduces the numeric value of future events, it is expected that the actual impact on the model will be similar or less than what is reported here. So even though the distribution of bleeds is only based on clinical expert opinion it is not critical for the result of this analysis.

The budget impact analysis assumes a slow market uptake if andexanet alfa is recommended as standard treatment. After five years the market uptake is expected to be 25 %. If the treatment is not recommended, there is expected to be an even slower market uptake which in year five is expected to be 5 %. [redacted] As a steep uptake in the Danish setting is not expected, the budget impact in the regions will therefore develop slowly both with and without a recommendation. The additional costs in the regions ranges from 728.590 DKK in year one to 5.342.994 DKK in year five if andexanet alfa is recommended vs. not recommended based on a patient size of 220. The specific patient population in Denmark has been estimated in the protocol as between 160-280 patients yearly. The span in patient population was addressed in sensitivity analyses and the budget impact for 160 patients ranges from 485.727 DKK in year one to 3.885.814 DKK in year five if andexanet alfa is recommended vs. not recommended. For 280 patients it ranges from 850.022 DKK to 6.800.174 DKK. Even though there is a difference in budget impact based on different patient populations, the slow uptake will still restrict the budget impact. The uptake can be difficult to foresee and it is [redacted] If the uptake of andexanet alfa will differ from the estimates included in this analysis the budget impact will of course change accordingly.

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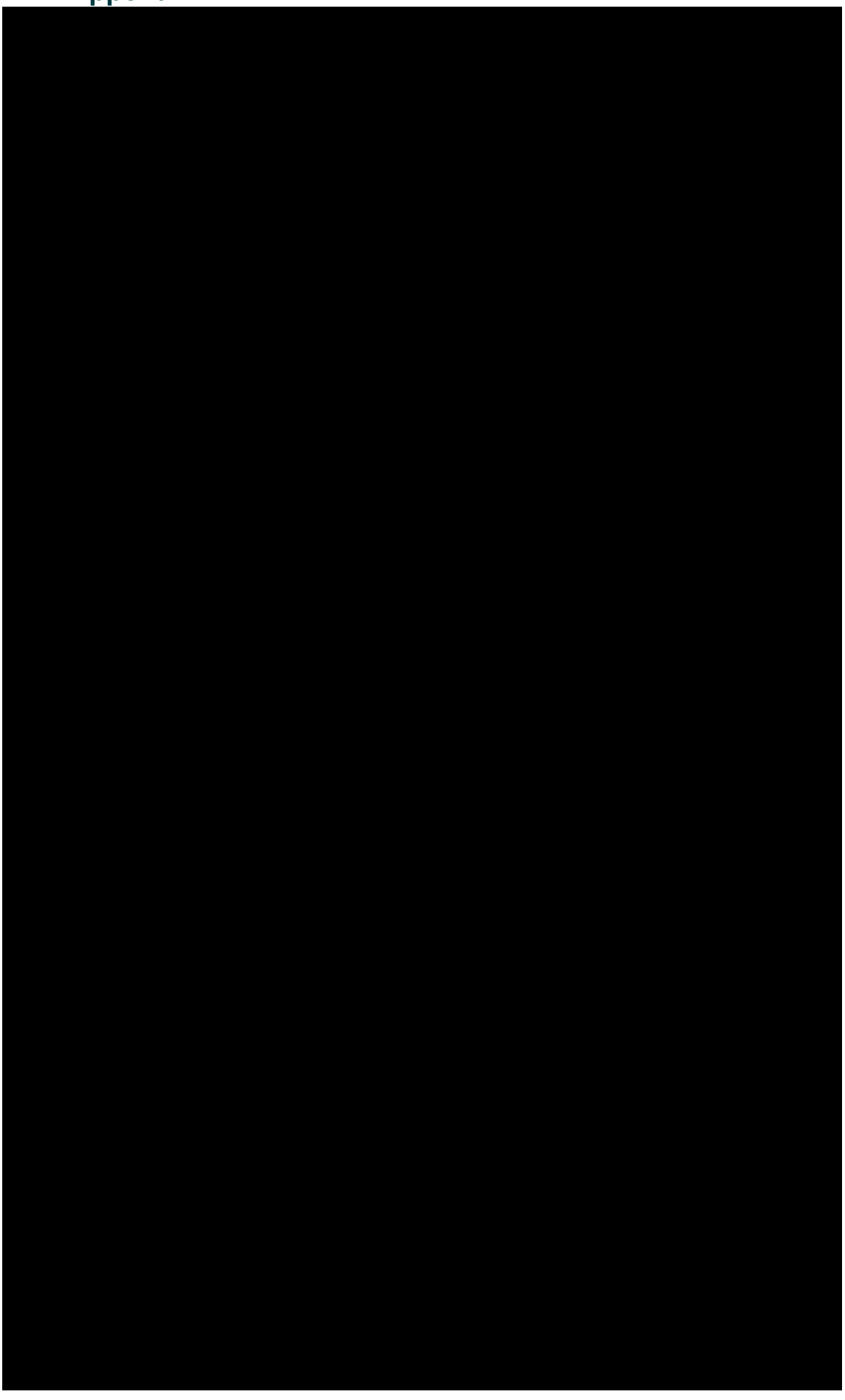
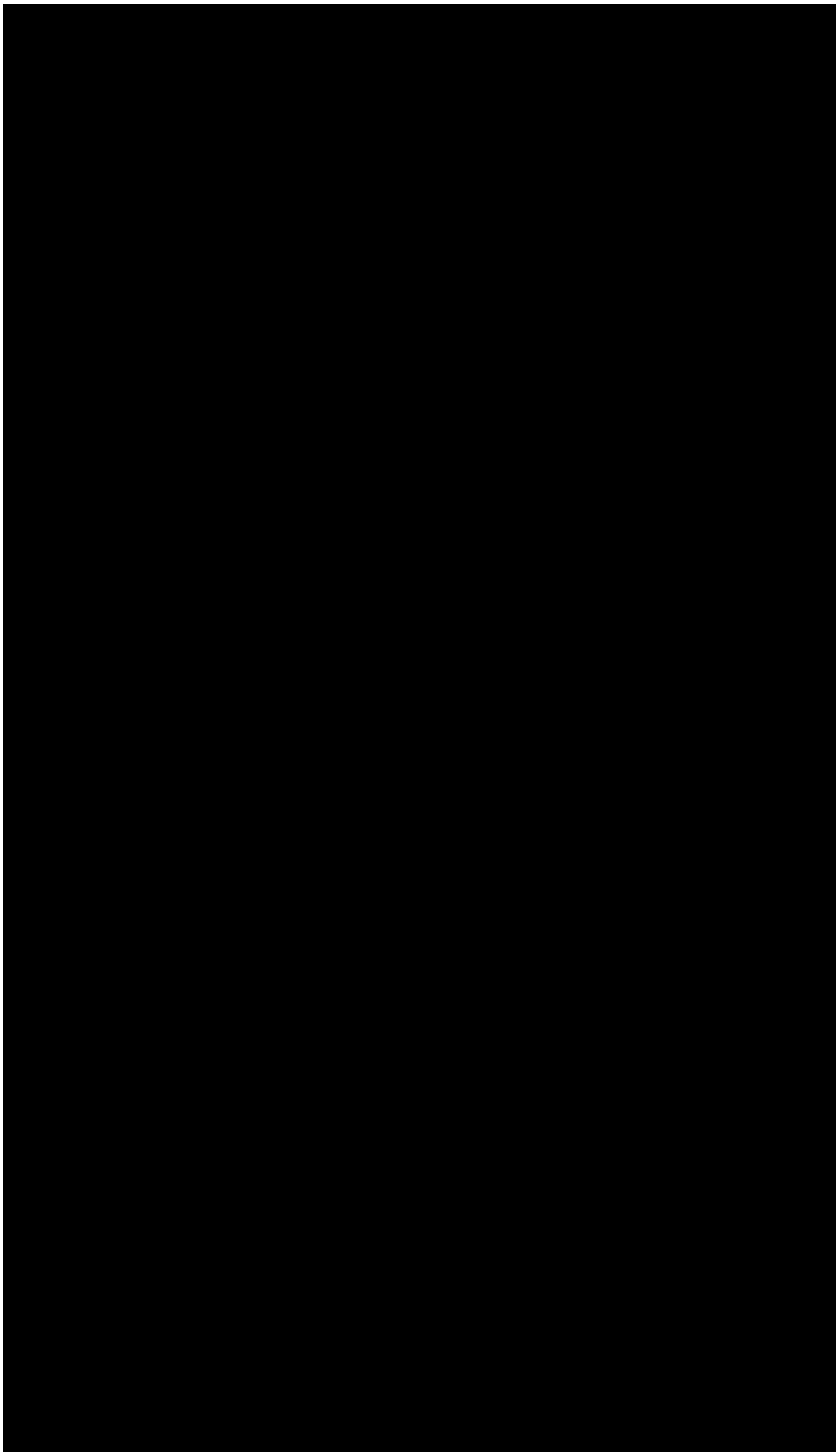
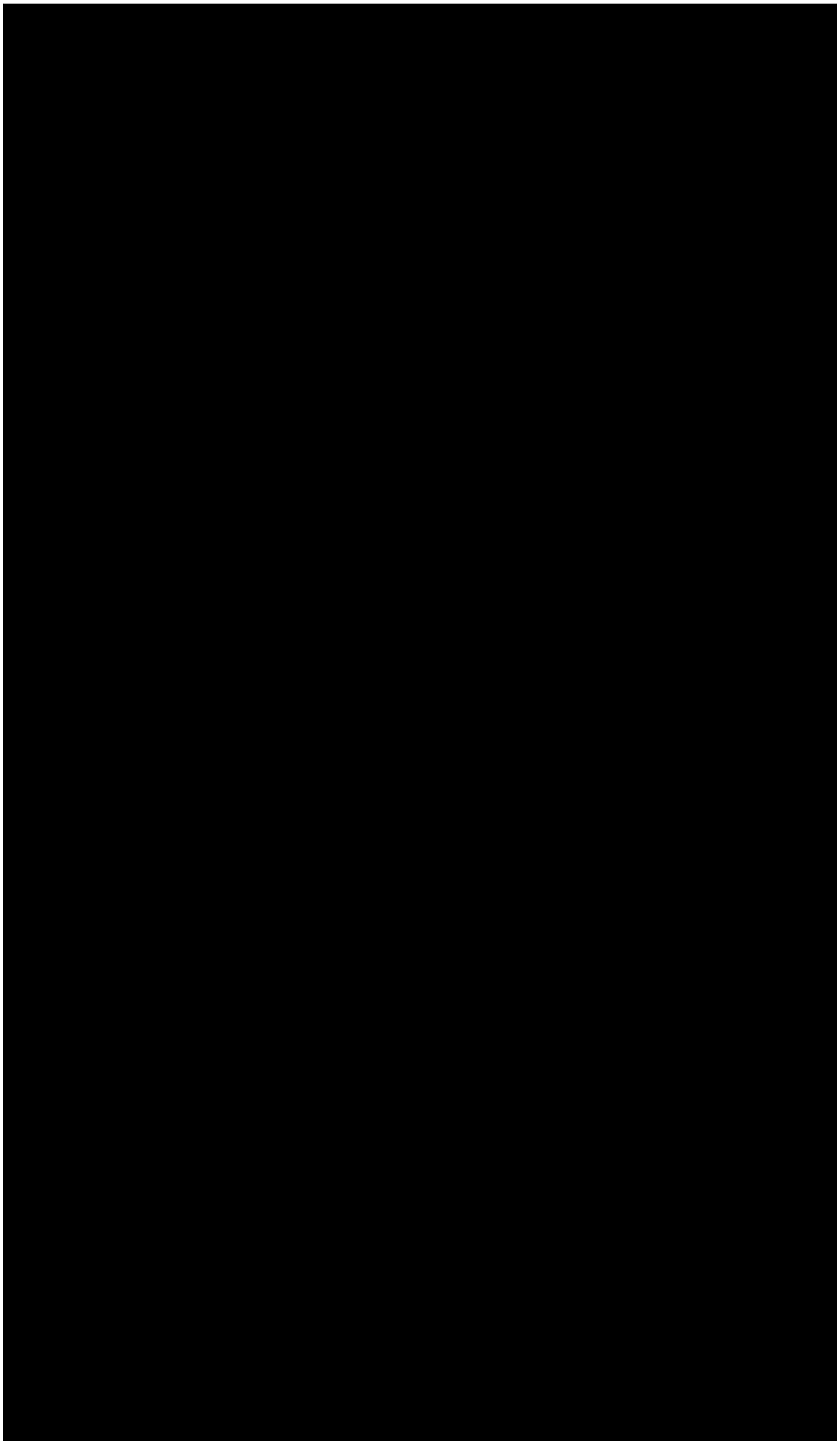
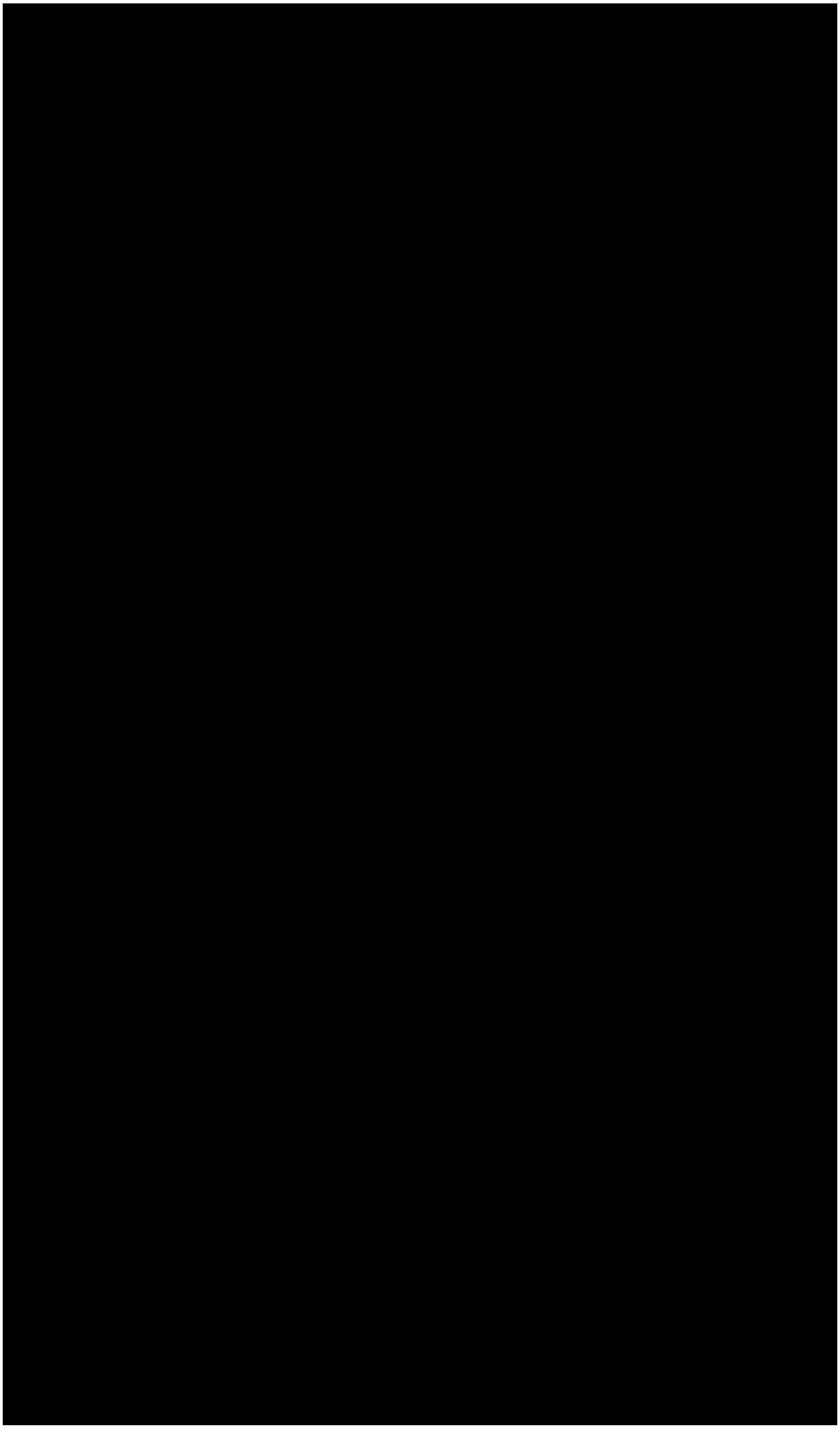
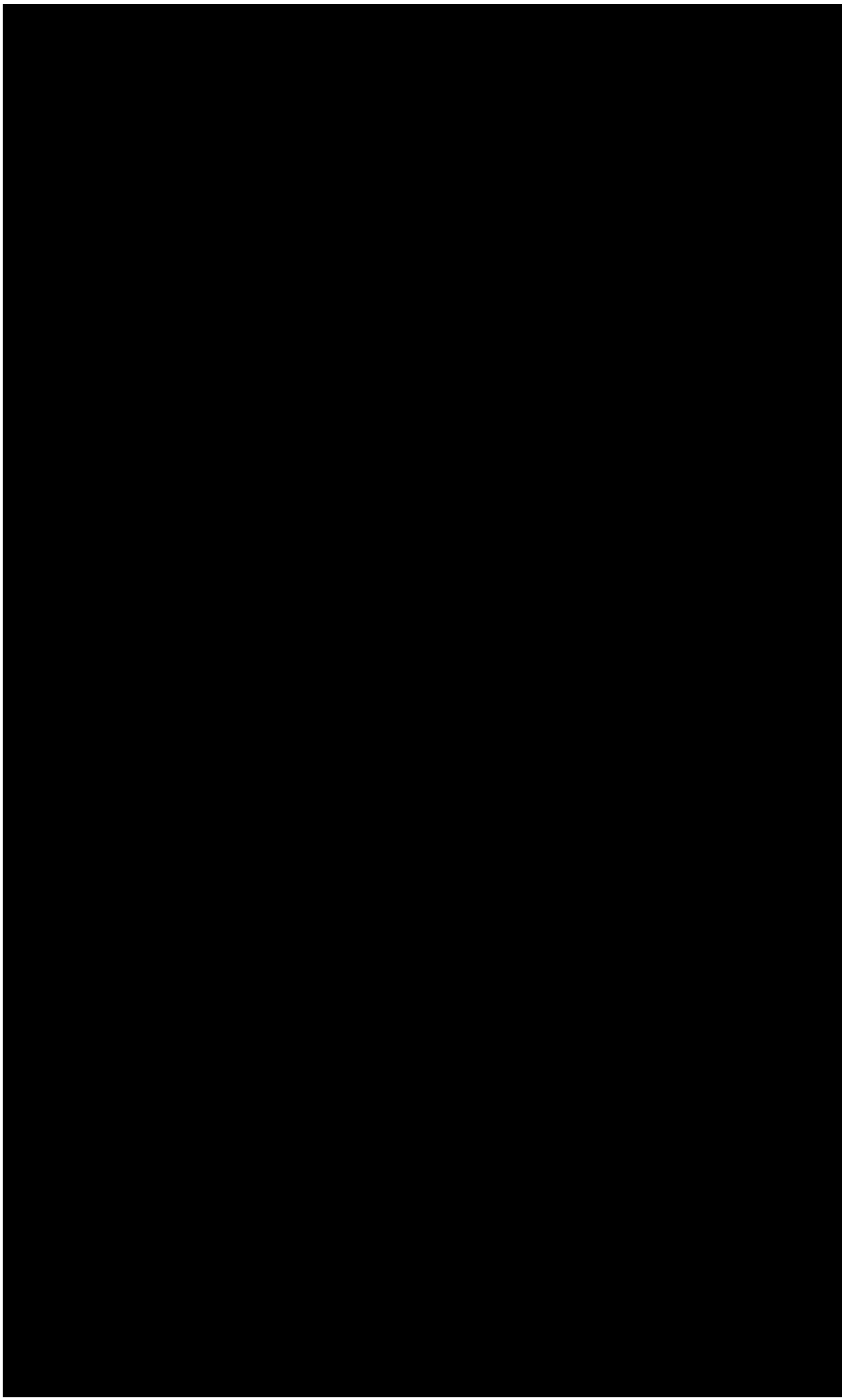
11. Appendix

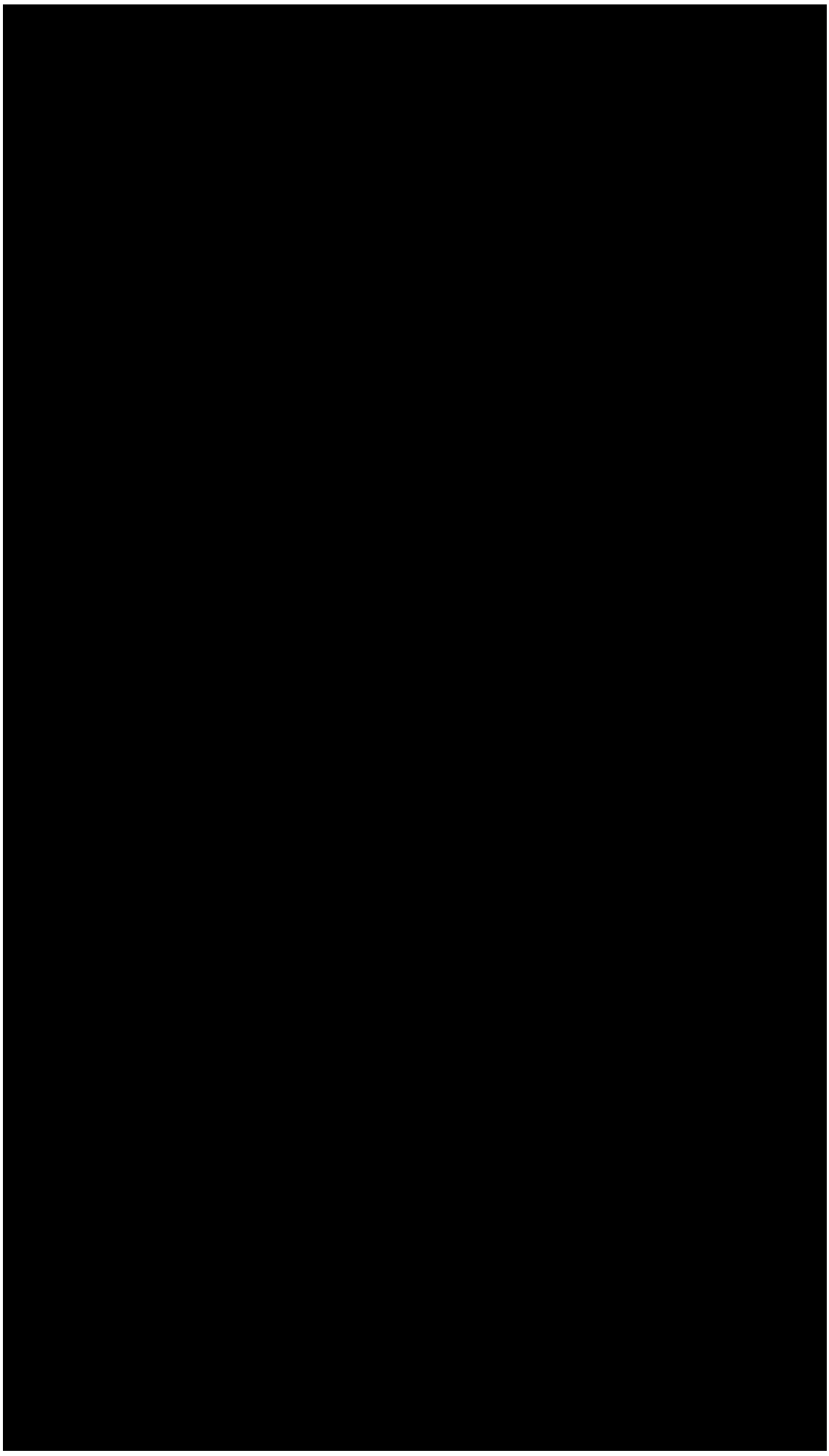


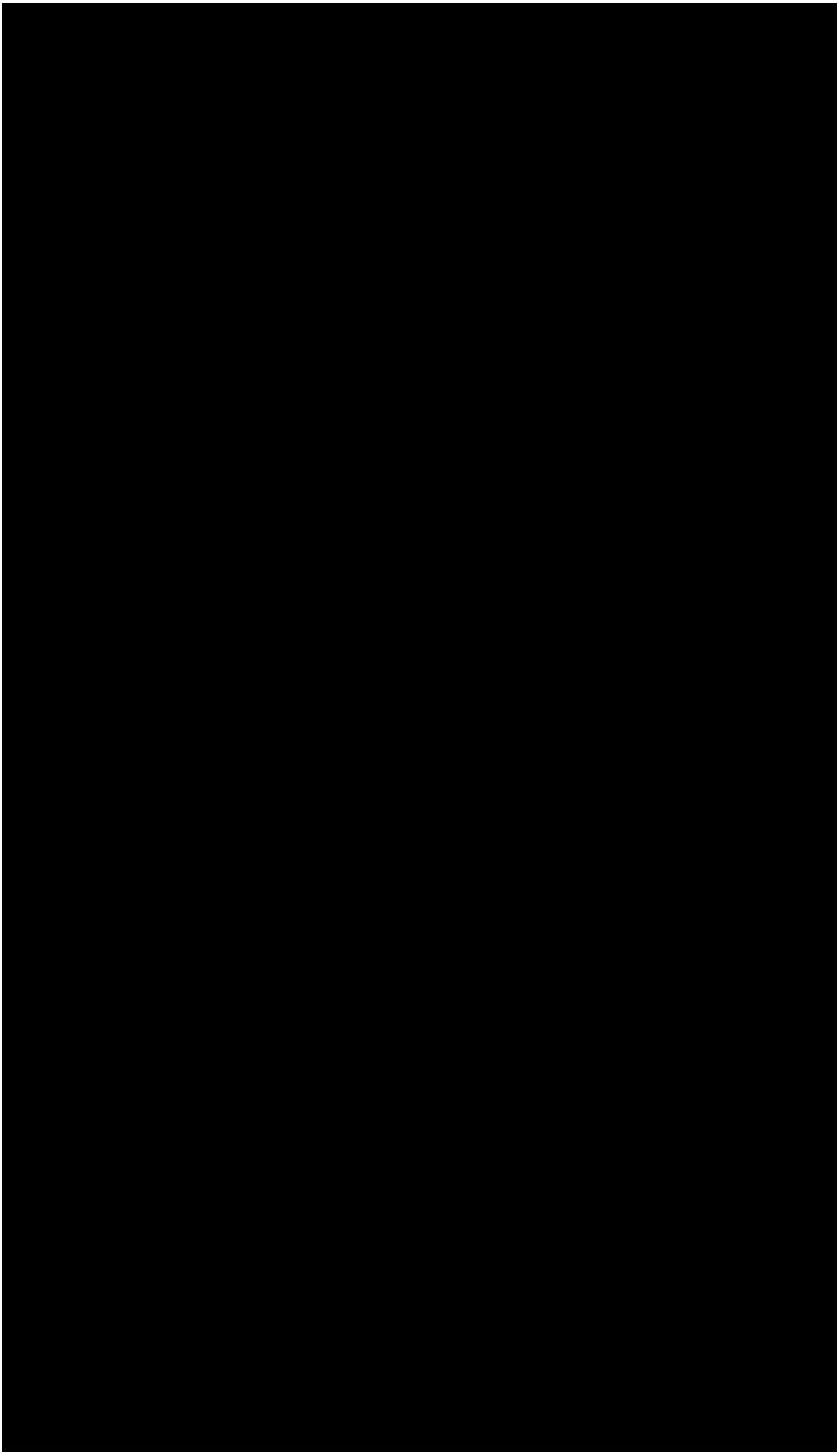


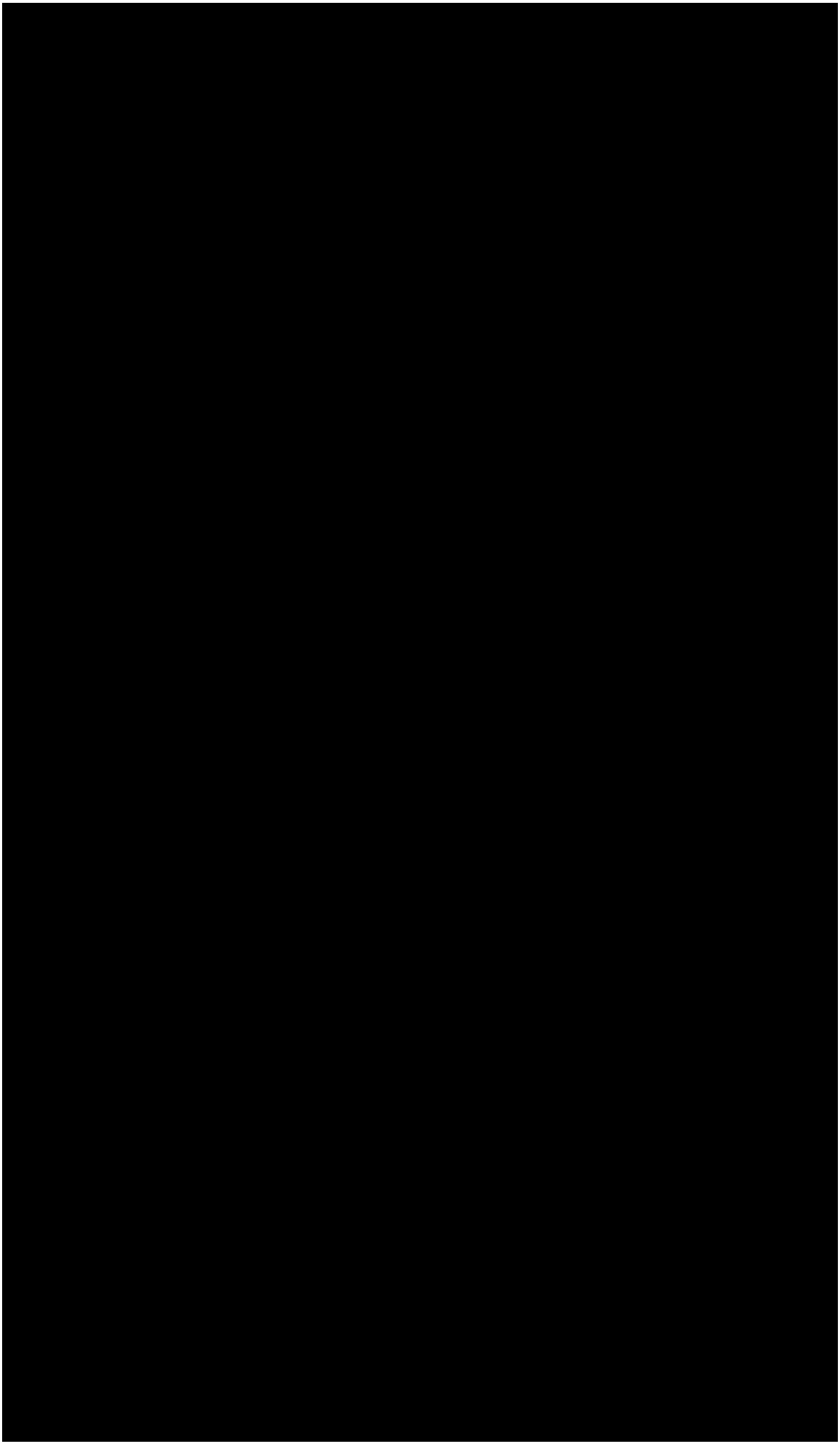


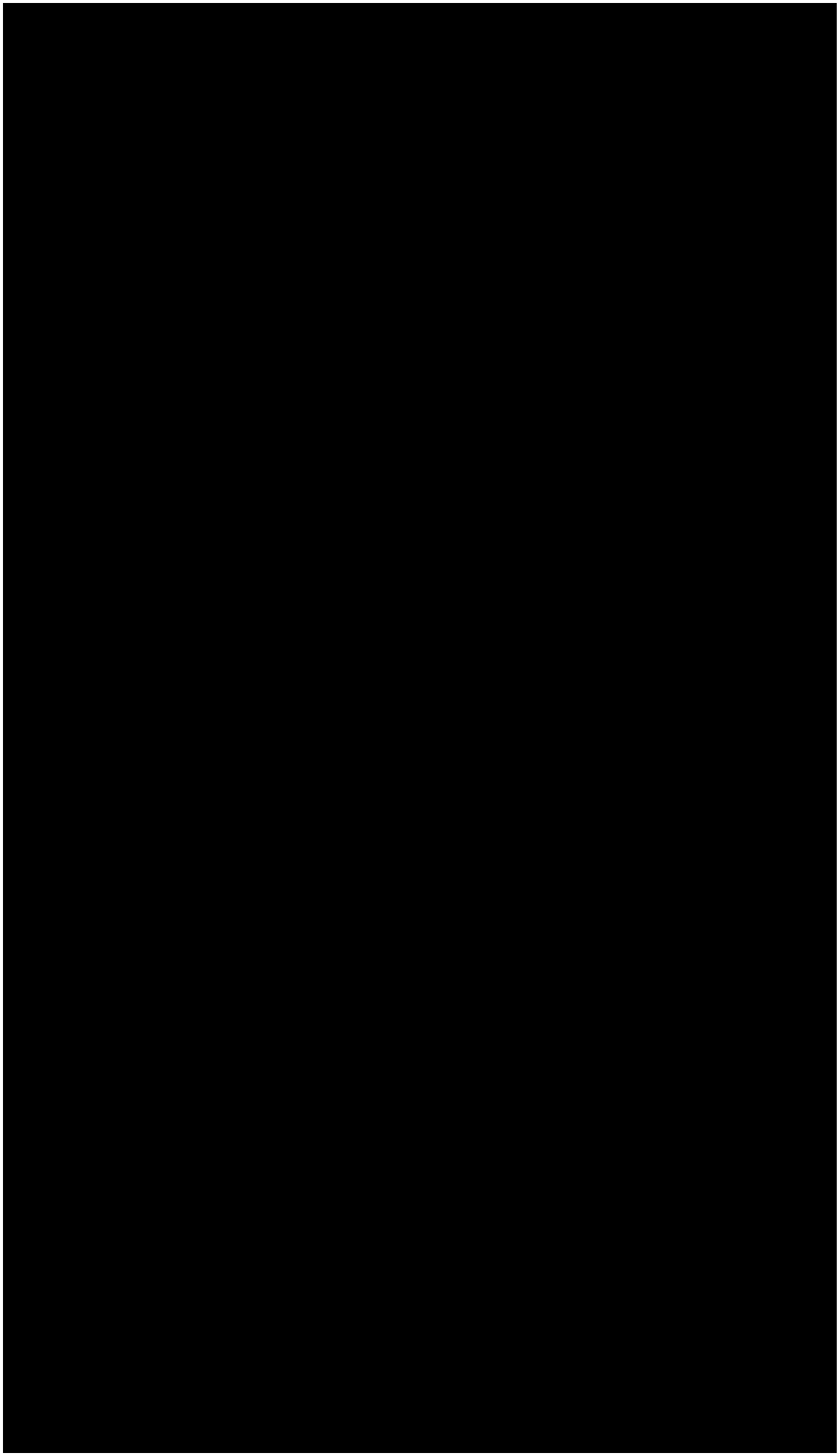


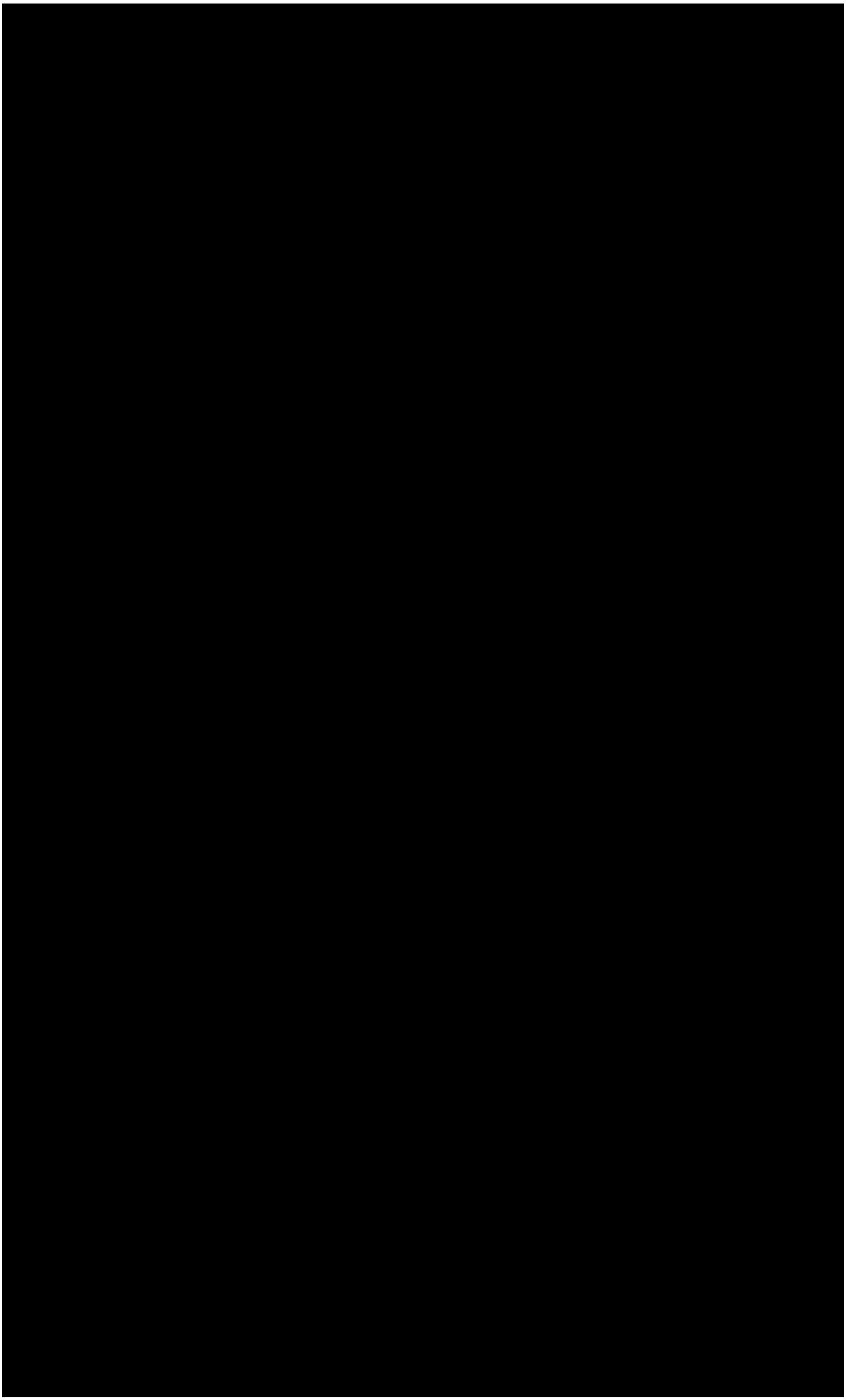


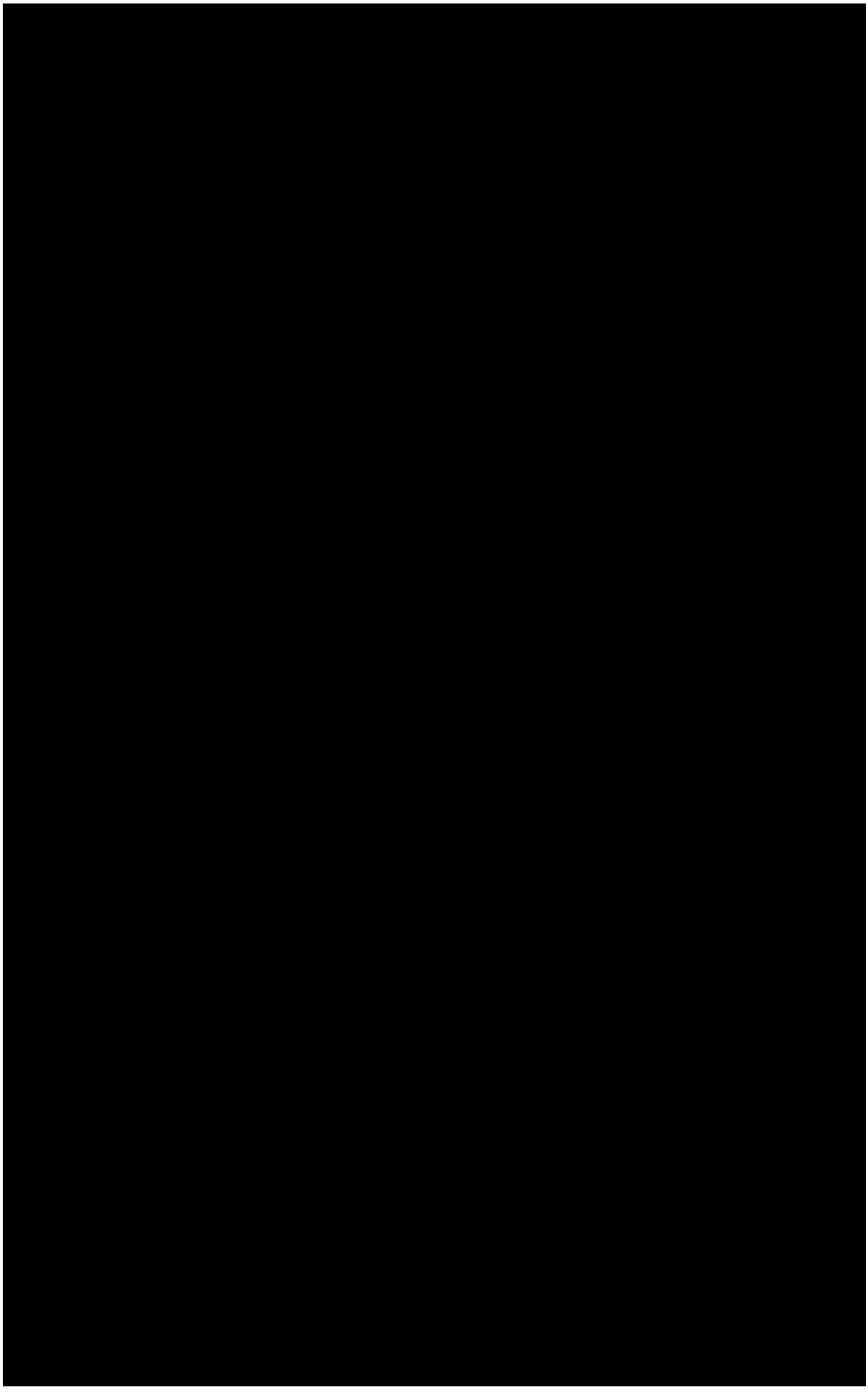


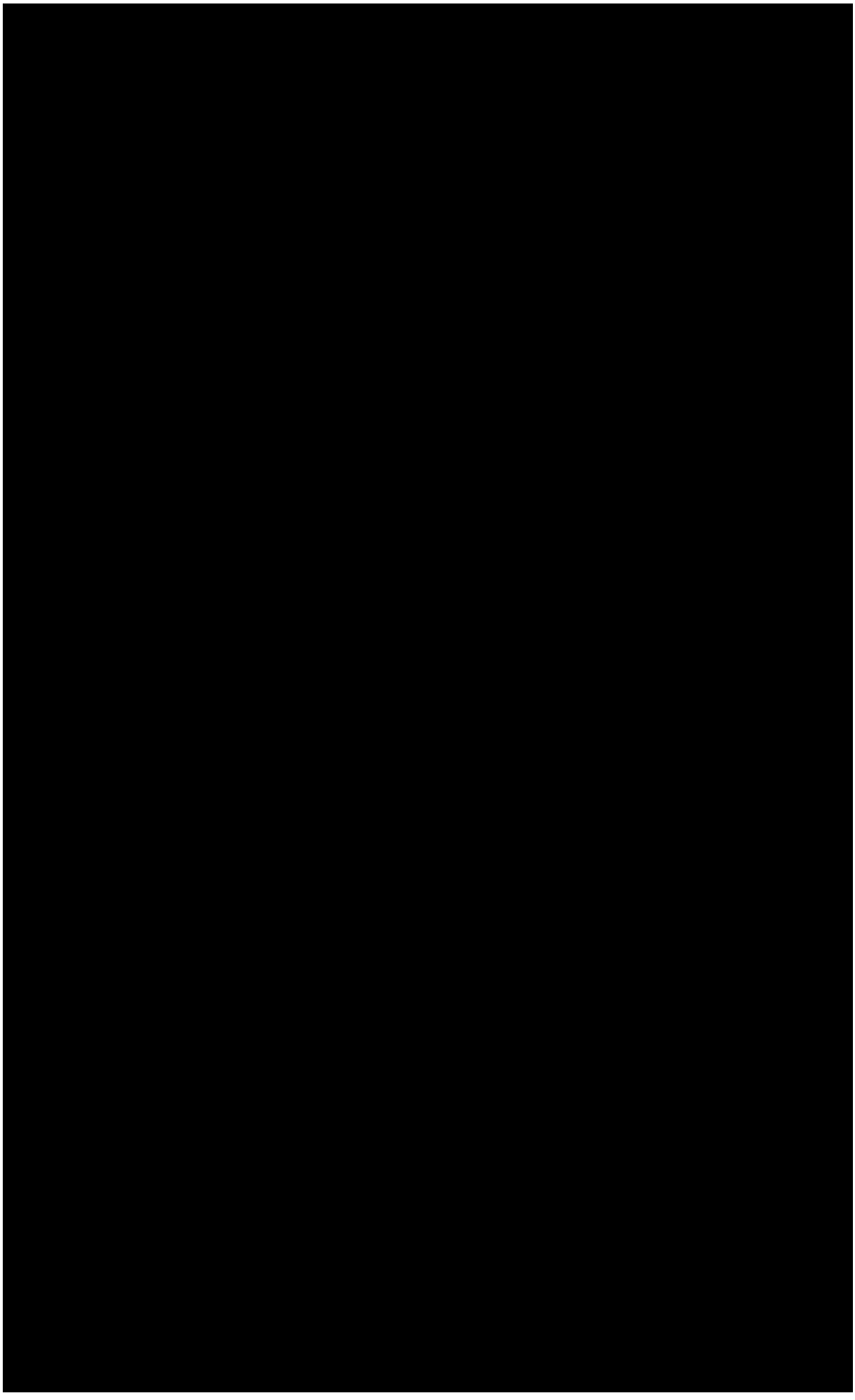


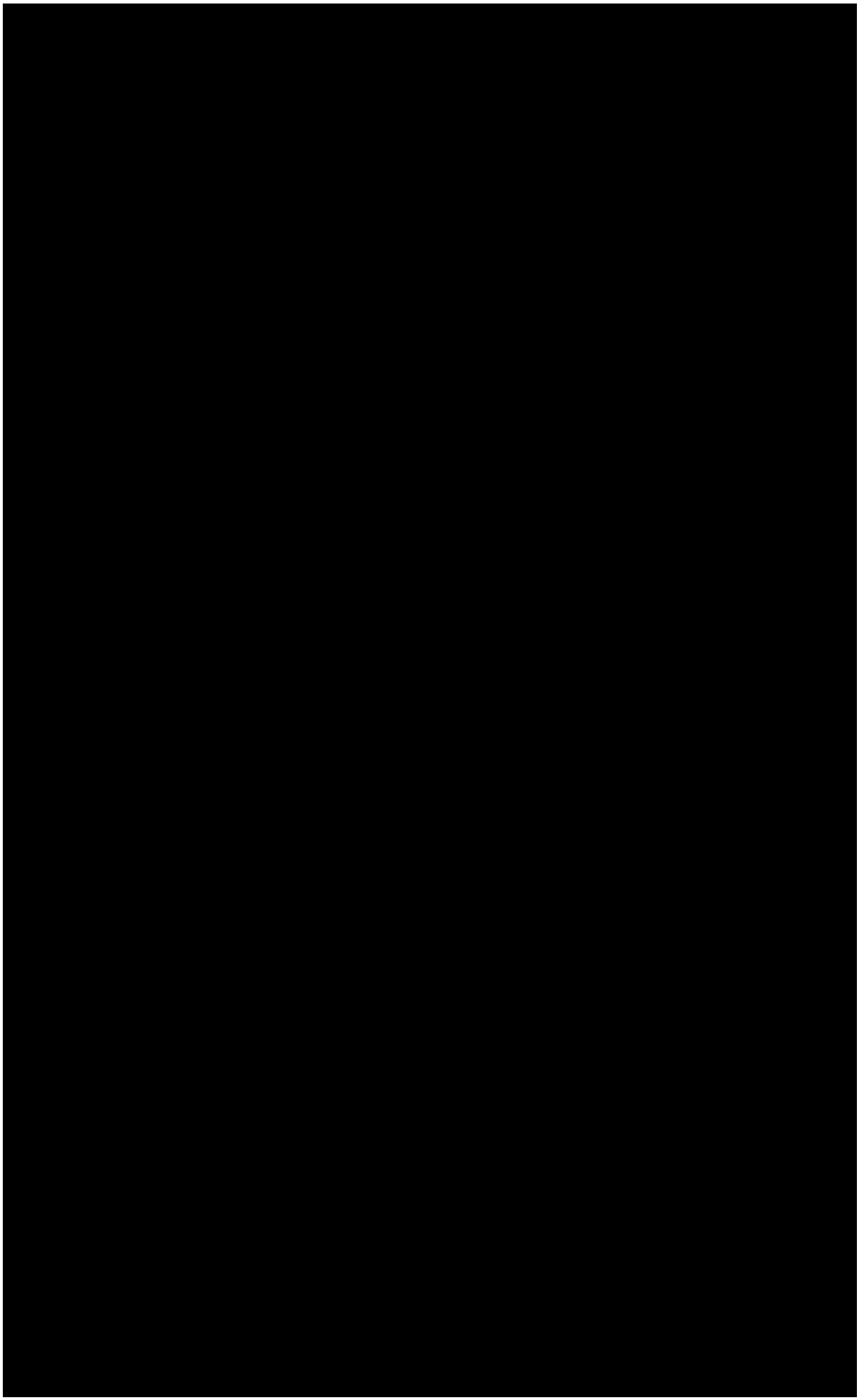


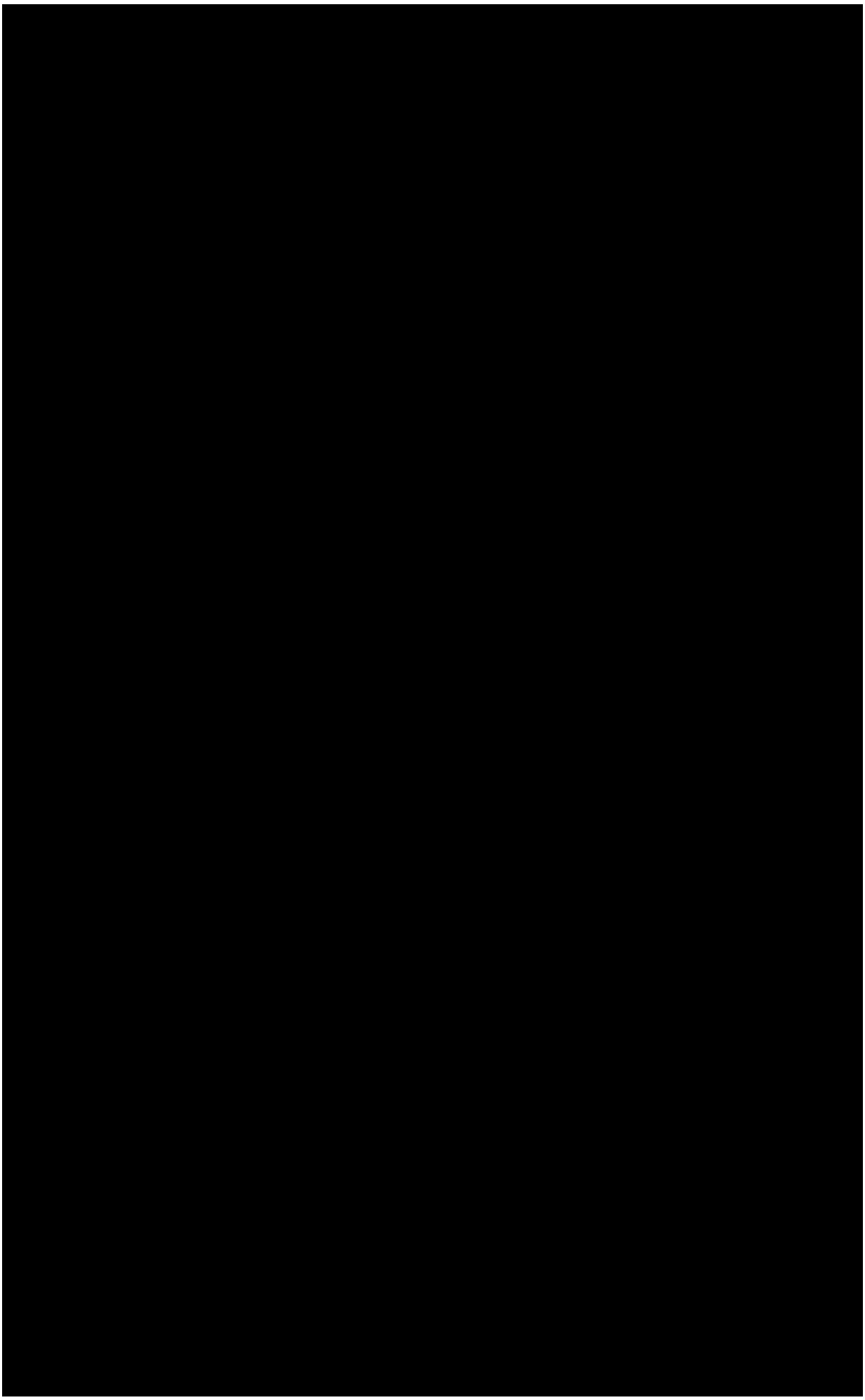


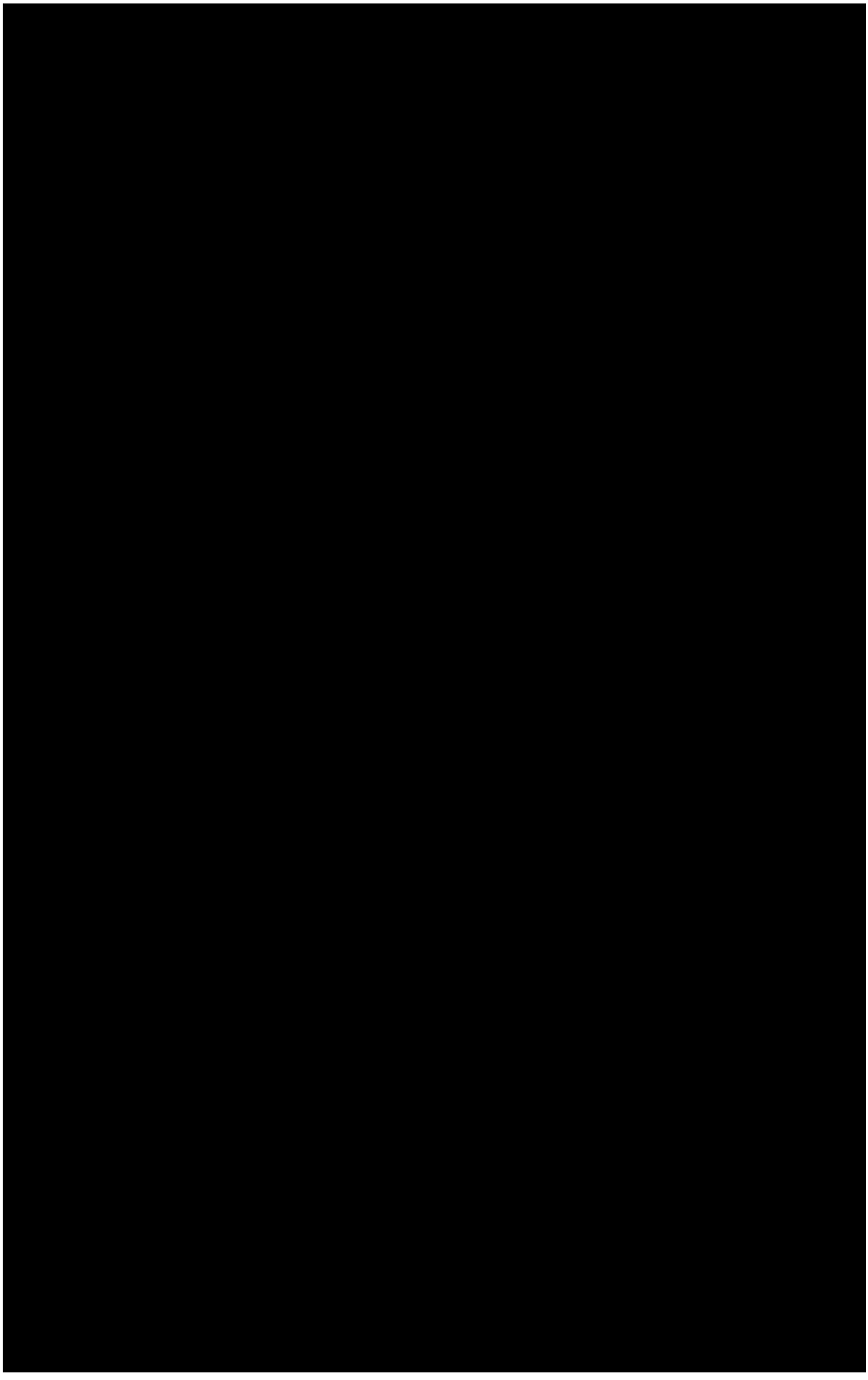


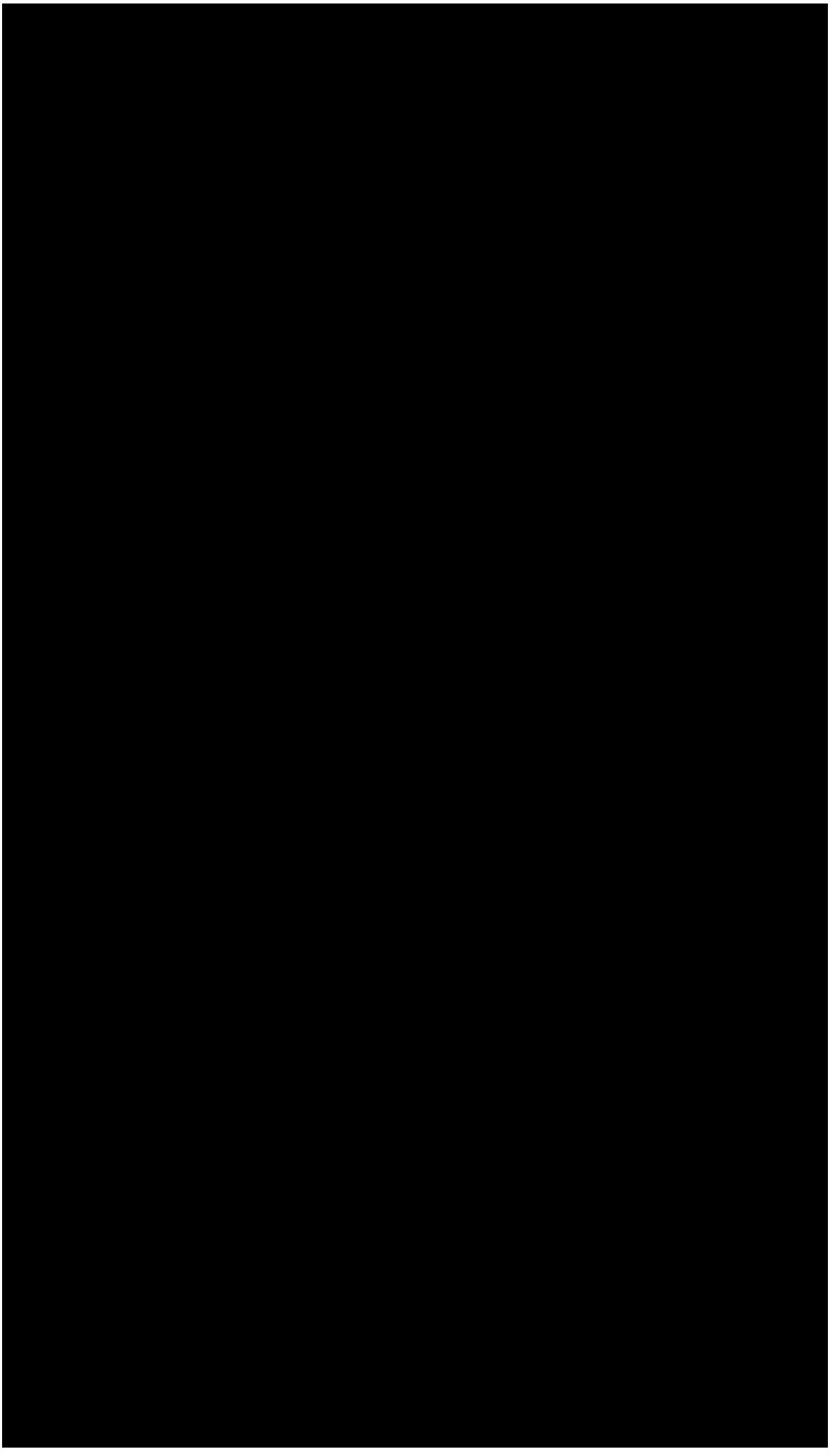


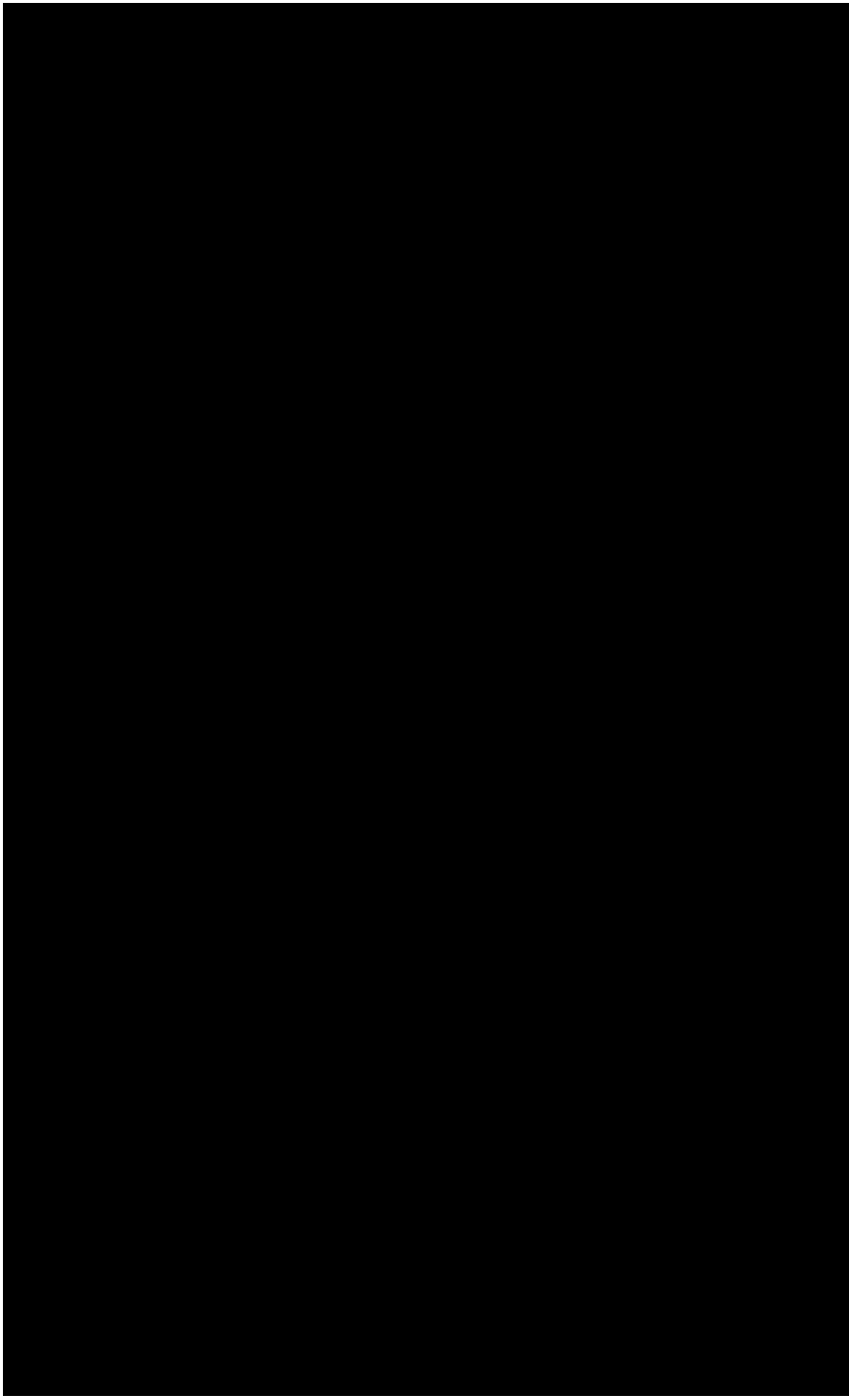












Medicinrådet

Medicinrådets protokol for vurdering af andexanet alfa til patienter som modtager direkte faktor Xa-hæmmer og har livstruende eller ukontrolleret blødning

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser kan anbefales som mulig standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Om protokollen

Protokollen er grundlaget for Medicinrådets vurdering af et nyt lægemiddel. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i den endelige ansøgning, og som Medicinrådet skal basere sin vurdering på.

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	2. januar 2020
Ikrafttrædelsesdato	7. januar 2020
Dokumentnummer	68234
Versionsnummer	1.0

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil ansøgende virksomhed få besked.

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 7. januar 2020

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Ondexxya®
Generisk navn	Andexanet alfa
Firma	Portola Netherlands B.V.
ATC-kode	V03AB38
Virkningsmekanisme	Rekombinant modificeret variant af human faktor Xa, som kompetitivt kan binde faktor Xa-hæmmere, men ikke omdanne protrombin til trombin ligesom naturlig faktor Xa. Ophæver derved den antikoagulante virkning af faktor Xa-hæmmerne apixaban og rivaroxaban.
Administration/dosis	Leveres i hætteglas i pulverform der skal opløses i infusionsvæske. Dosis afhænger af dosering af faktor Xa-hæmmer.
EMA-indikation	Til voksne patienter der behandles med en direkte faktor Xa (FXa)-inhibitor (apixaban eller rivaroxaban), når der er behov for revertering af antikoagulation på grund af livstruende eller ukontrolleret blødning. Lægemidlet har en betinget EMA-godkendelse, og ansøger er blevet pålagt at udføre et randomiseret fase 3-studie overfor nuværende standardbehandling.

2 Forkortelser

AK-behandling: Antikoagulationsbehandling

CI:	Konfidensinterval
DOAK:	Direkte orale antikoagulantia
EMA:	*European Medicines Agency*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
ISTH:	*International Society on Thrombosis and Haemostasis (ISTH)*
OR:	*Odds ratio*
PKK:	Protrombinkomplexkoncentrat
RR:	Relativ risiko

3 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af andexanet alfa som mulig standardbehandling til voksne patienter, der behandles med en direkte faktor Xa (FXa)-inhibitor (apixaban eller rivaroxaban), når der er behov for revertering af antikoagulation på grund af livstruende eller ukontrolleret blødning. I protokollen angives en definition af population(er), komparator(er) og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende andexanet alfa, modtaget den 25. oktober 2019.

Protokollen danner grundlag for den endelige ansøgning for vurdering af andexanet alfa sammenlignet med dansk standardbehandling (jf. afsnit 4.1). Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem andexanet alfa og protrombinkomplexkoncentrat (PKK) på basis af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 1). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

4 Baggrund

Blodets evne til at størkne, koagulation, er en nøje reguleret proces, som aktiveres ved vævsskader. Blodkoagulationen er kompleks og består af en kaskade af reaktioner, der aktiveres for at stoppe blødninger. Koagulationssystemet består både af en cellulærkomponent (blodplader) og en proteinkomponent (koagulationsfaktorer). I tillæg til koagulationsfaktorerne er der ligeledes en række proteiner, der fungerer regulerende for koagulationen. Normalt er der en balance mellem disse processer, som forhindrer omfattende blødninger eller uønsket koagulation. Ved ubalance i systemet vil man enten få en blødningstendens, så man bløder lettere, og blødningerne standser ikke så hurtigt som normalt, eller man kan få en øget risiko for blodpropper.

Antikoagulationsbehandling (AK-behandling) gives til patienter med en øget risiko for at danne blodpropper, f.eks.: 1) ved forebyggelse af slagtilfælde hos patienter med atrieflimmer; 2) ved behandling og sekundær forebyggelse af blodpropper eller; 3) ved forebyggelse af blodpropper for patienter der skal have lavet et ortopædkirurgisk indgreb [1]. De forskellige AK-behandlinger adskiller sig ved, hvor de indvirker på koagulationskaskaden for at modvirke, at patienten danner blodpropper. AK-behandling giver en øget blødningstendens, herunder en øget risiko for morbiditet og mortalitet som følge af alvorlige blødninger. Blødninger kan være alvorlige, hvis patienten mister meget blod, eller hvis blødningen opstår et kritisk sted, f.eks. i kraniet eller øjet.

Oral AK-behandling kan bestå af enten et direkte oralt antikoagulantium (DOAK) eller en vitamin K-antagonist (VKA-behandling). Risikoen for en alvorlig blødning varierer mellem forskellige AK-behandlinger. Generelt rapporterer studier lavere blødningsfrekvens, og særligt en reduktion i intrakranielle blødninger, ved DOAK-behandling end ved VKA-behandling [2]. På baggrund af at DOAK-behandling har vundet stort indpas, er DOAK-associerede blødninger dog en voksende problematik.

Randomiserede undersøgelser og observationelle studier har fundet, at alvorlige blødninger sker i 2-3,5 % af alle patienter pr. år behandlet med DOAK. Risikoen for intrakranielle blødninger anslås til ca. 0,3-0,5 % pr. patientår [3,4]. Gastrointestinale blødninger udgør op til 56 %, og intrakranielle blødninger udgør en mindre andel, ca. 8-16 %, af de alvorlige blødninger hos patienter i DOAK-behandling [1].

Patienter i AK-behandling, der får en alvorlig blødning, har en stærkt øget dødelighed og risiko for trombose. Patienter med atrieflimren i behandling med DOAK, der får en alvorlig blødning, har en dødelighed på mellem 15-20 % indenfor 30 dage, og dødeligheden er op til ca. 50 % for patienter med intrakranielle

blødninger [1]. Den høje dødelighed skyldes patienternes underliggende sygdom, selve blødningen og den øgede risiko for blodpropper ved seponering af AK-behandlingen.

Andexanet alfa er rettet mod revertering af en undergruppe af DOAK, kaldet direkte faktor Xa-hæmmere (FXa-hæmmer), herunder specifikt de to mest anvendte DOAKs i Danmark, rivaroxaban og apixaban. Fagudvalget anslår, at ca. 80.000 patienter er i behandling med rivaroxaban og apixaban. Under antagelse af en hændelsesrate for alvorlige blødninger på 2-3,5 % vil 1.600-2.800 patienter årligt få alvorlig direkte FXa-hæmmerassocieret blødning. Heraf vil kun en lille andel have livstruende eller ukontrollerede blødninger og dermed være kandidater til akut reverteringsbehandling. Fagudvalget anslår, at dette gælder for 10 %, svarende til 160-280 patienter årligt. Fagudvalget ønsker at fremhæve, at dette estimat er forbundet med nogen usikkerhed, særligt da estimatet forudsætter, at anvendelsen af andexanet alfa udelukkende forbeholdes til den godkendte indikation. Fagudvalget ser risiko for indikationsskred ved behandlingen og vil derfor også kommentere på dette i sin vurderingsrapport (jf. afsnit 8, Andre overvejelser).

4.1 Nuværende behandling

Behandling af alvorlig blødning indsættes tidligst muligt og retter sig mod at stoppe blødningen med symptomatisk behandling, samtidig med at kirurgisk kontrol af blødningen søges sikret. Derudover overvejes revertering af pågående AK-behandling ud fra en individuel vurdering af fordele/risici relateret til blødningens karakter og til indikationen for lægemidlet, idet revertering fjerner den beskyttende antikoagulerende effekt, og derved øges risikoen for blodpropper.

Revertering af AK-behandling kan være specifik eller uspecifik. Til specifik revertering kan anvendes en antidot til direkte neutraliserende effekt af AK-behandlingen, hvis en sådan er tilgængelig. Til uspecifik revertering kan anvendes prohæmostatika (f.eks. tilførsel af koagulationsfaktorer) til hel eller delvis normalisering af koagulationen.

Direkte FXa-hæmmere (apixaban, rivaroxaban) har ikke tidligere haft en specifik antidot. Den nuværende behandling af alvorlige blødninger associeret med direkte FXa-hæmmere kan bestå af følgende elementer: Stop behandling med FXa-hæmmer, foretag relevant laboratorieundersøgelse, indled understøttende behandling med blodprodukter, væskebehandling, supplér eventuelt med lægemidler til at hæve blodtrykket, tranexamsyre eller lokal hæmostatika. Ved synlig blødning foretages kirurgisk kontrol af blødning. Denne indsats kaldes herefter samlet ”understøttende behandling”. Derudover overvejes uspecifik revertering af den antitrombotiske behandling ved at give PKK 25-50 IE/kg [5,6].

Indikationen for PKK er: ”behandling af blødning og perioperativ profylakse af blødning ved erhvervet mangel på protrombinkompleks-koagulationsfaktorer, som f.eks. ved mangel forårsaget af behandling med vitamin K-antagonister (*red. VKA-behandling*) eller i tilfælde af overdosering med vitamin K-antagonister, når der kræves en hurtig korrektion af mangeltilstanden” [7].

PKK er primært tiltænkt revertering af VKA-behandlede patienter, hvor dannelsen af protrombinkompleks-koagulationsfaktorer er hæmmet. Hos patienter behandlet med direkte FXa-hæmmer opstår der en erhvervet funktionel mangel på koagulationsfaktoren Xa (protrombinkompleks-koagulationsfaktor), fordi faktor Xa bindes af FXa-hæmmerne. Dermed vurderer fagudvalget også, at anvendelse af PKK til patienter behandlet med FXa-hæmmere falder indenfor indikationen. Det er vist, at tilførslen af PKK kan genetablere koagulationen, målt ved at trombindannelsen normaliseres efter indgivelsen af PKK [8]. Anvendelse af PKK ved direkte FXa-hæmmerassocierede blødninger betragtes derfor farmakologisk velbegrundet. Ansøger har tilkendegivet, at de mener, at PKK-behandling er en off-label-behandling, men med ovenstående argumenter mener fagudvalget, at PKK udgør standardbehandlingen i Danmark, og at anvendelse af PKK til FXa-hæmmerassocierede blødninger falder indenfor den godkendte indikationen.

4.2 Det nye lægemiddel

Andexanet alfa er indiceret til voksne patienter, der behandles med en direkte FXa-hæmmer (apixaban eller rivaroxaban), når der er behov for revertering af antikoagulation på grund af livstruende eller ukontrolleret blødning. Andexanet alfa er en rekombinant modificeret variant af human faktor Xa, som kompetitivt kan binde faktor Xa-hæmmere og dermed ophæve virkningen af direkte FXa-hæmmere. Andexanet alfa er derudover modificeret således, at lægemidlet ikke – ligesom naturlig FXa – kan omdanne protrombin til trombin, da dette ville medføre en stærk protrombotisk effekt. Derudover kan andexanet alfa binde til tissue factor pathway inhbitor (TFPI), hvis funktion er at hæmme de tidlige stadier af koagulationen. Interaktionen mellem andexanet alfa og TPFI samt den kliniske betydning heraf er ufuldstændigt karakteriseret [9]. Det er derfor uklart, om interaktionen mellem andexanet alfa og TFPI kan medvirke til en uønsket protrombotisk effekt (se afsnit 8, Andre overvejelser) [9].

Andexanet alfa kan gives i tillæg til den understøttende behandling, jf. afsnit 4.1, efter et doseringsprogram, der afhænger af dosering af FXa-hæmmeren samt tid siden sidste dosering. Ud fra dette bestemmes det, om patienten skal have behandling med en lav eller høj dosis af andexanet alfa. Andexanet alfa gives som en intravenøs bolusinfusion af ca. 30 mg/min. over 15 minutter (lav dosis) eller 30 minutter (høj dosis) efterfulgt af kontinuert infusion af 4 mg/min. (lav dosis) eller 8 mg/min. (høj dosis) i 2 timer. Hvis dosis af direkte FXa-hæmmer er ukendt, og tid siden sidste dosis er ukendt, gives der som udgangspunkt en høj dosis andexanet alfa. Fagudvalget vurderer, at over halvdelen af patienterne vil blive behandlet med højdosis andexanet alfa, da det i den akutte situation vil gælde, at enten dosis af FXa-hæmmer eller tid siden sidste dosis vil være ukendt.

5 Kliniske spørgsmål

5.1 Klinisk spørgsmål 1

Hvad er værdien af andexanet alfa sammenlignet med protrombinkomplexkoncentrat til patienter, som modtager direkte faktor Xa-hæmmer og har livstruende eller ukontrolleret blødning?

Population
Patienter som modtager direkte FXa-hæmmer (apixaban og rivaroxaban) og har livstruende eller ukontrolleret blødning.

Intervention
Andexanet alfa i.v. givet i henhold til doseringsprogram med lav dosis eller høj dosis, baseret på dosis af apixaban eller rivaroxaban, samt hvor længe siden sidste dosis blev taget, jf. afsnit 4.2.

Herudover kan foretages understøttende behandling situationsbestemt.

Komparator
Protrombinkomplexkoncentrat (PKK) 25-50 IE/kg, jf. afsnit 4.1.

Herudover kan foretages understøttende behandling situationsbestemt.

Effektmål
Se tabel 1 for effektmål.

5.2 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, den retningsgivende mindste klinisk relevante forskel, en evt. justeret mindste klinisk relevant forskel og effektmålsgruppe. I forbindelse med justeringen af Medicinrådets metodehåndbog, som trådte i kraft pr. 1. januar 2019, vil absolutte effektforskelle fremover blive kategoriseret ud fra konfidensintervaller (tabel 3, side 29 i metodehåndbogen). Det er derfor nødvendigt at foretage en justering af den mindste klinisk relevante forskel. Den *retningsgivende* mindste klinisk relevante forskel er fremkommet på samme måde som under den gamle metode og afspejler den mindste forskel, fagudvalget vurderer er klinisk relevant. Når lægemidlets værdi for det enkelte effektmål skal kategoriseres, vil grænsen for konfidensintervallet blive sammenholdt med den *justerede* mindste klinisk relevante forskel. Den justerede værdi vil være det halve af den retningsgivende værdi i de tilfælde, hvor et konfidensinterval forventes at være tilgængeligt. Rationalet for denne tilgang er at sikre, at alle værdier i konfidensintervallet ligger tættere på den *retningsgivende MKRF* end på 'ingen forskel' (absolut effektforskel på 0). Eller sagt på en anden måde – alle de sandsynlige værdier for effekten er tættere på en klinisk relevant effekt end på 'ingen effekt'.

Tabel 1. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel (retningsgivende og evt. justeret) samt indplacering i de tre effektmålsgrupper ("dødelighed" "livskvalitet, alvorlige symptomer og bivirkninger" og "ikkealvorlige symptomer og bivirkninger").

Effektmål*	**Vigtighed**	**Effektmålsgruppe**	**Måleenhed**	**Retningsgivende mindste klinisk relevante forskel**	**Justeret mindste klinisk relevante forskel**
Dødelighed	Kritisk	Dødelighed	Andel patienter der dør indenfor 30 dage	2 %-point	1 %-point
Komplikationer - funktionsnedsættelse (kun patienter med intrakranielle blødninger)	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Forskel i ændring målt på modificeret Rankinskala (MRS) fra baseline til efter 30 dage	4 %-point	2 %-point
Hæmostasekontrol (kun for patienter uden intrakranielle blødninger)	Vigtigt	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter der opnår effektiv hæmostase indenfor 48 timer, jf. ISTH-kriterier	5 %-point	2,5 %-point
Bivirkningsprofil og sikkerhedsaspekter	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter der får en trombo-embolisk hændelse indenfor 30 dage	Ikke relevant, se nedenstående	-
			Kvalitativ gennemgang af bivirkningsprofil og sikkerheds-aspekter	-	-
Livskvalitet	Vigtigt	Livskvalitet, alvorlige symptomer og bivirkninger	Forskel i ændring i EQ-5D index score	≥ 0,10 i index score	-

* For alle effektmål ønskes data med længst mulig opfølgningstid.

For alle effektmål ønskes både absolutte og relative værdier, jf. ansøgningsskemaet. Der ønskes både punktestimater og konfidensintervaller (for de absolutte værdier ønskes dog ikke konfidensintervaller, hvor

metoderne til beregning af disse ikke er veldefinerede). For de absolutte værdier, hvor der kan beregnes konfidensintervaller efter veldefinerede metoder, vurderes den kliniske relevans (værdi), jf. tabel 3 i Medicinrådets håndbog for vurdering af nye lægemidler. For de relative værdier vurderes den kliniske relevans (værdi), jf. væsentlighedskriterierne beskrevet i Medicinrådets håndbog. De relative effektestimater skal angives i relativ risiko (RR) eller hazard ratio (HR). Hvis studierne rapporterer en odds ratio (OR), skal denne transformeres til relativ risiko, jf. appendiks 2 i Medicinrådets håndbog. Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

5.3 Kritiske effektmål

5.3.1 Dødelighed

Dødelighed efter 30 dage

Det primære formål med behandling af ukontrollerede og livstruende blødninger er at forhindre, at patienten dør af blødningen. Dødelighed defineres som tiden fra randomisering eller opstart af behandling til død, uanset årsag. Til trods for behandling med understøttende behandling har patienter med ukontrollerede og livstruende blødninger en meget høj dødelig, der er opgjort til mellem 15-20 % for patienter med atrieflimren og er i behandling med direkte FXa-hæmmer og op til ca. 50 % for patienter med alvorlige intrakranielle blødninger [1,10]. Fagudvalget fastsætter på denne baggrund den mindste klinisk relevant forskel til 2 %-point.

5.3.2 Komplikationer – funktionsnedsættelse (kun for patienter med intrakranielle blødninger)

Modificeret Rankinskala efter 30 dage

Fagudvalget ønsker at anvende modificeret Rankinskala (MRS) med henblik på at belyse, hvordan patienter med intrakranielle blødninger klarer sig efter hændelsen. Det vurderes særligt vigtigt med henblik på at vurdere, hvorvidt de patienter, der overlever intrakranielle blødninger, opnår et acceptabelt eller forbedret funktionsniveau efter deres rehabiliteringsforløb. Fagudvalget ønsker derfor effektmålet opgjort samlet for alle patienter med intrakranielle blødninger samt selvstændigt kun for de patienter, der overlever deres blødning.

MRS er det mest anvendte kliniske effektmål i kliniske forsøg med patienter, der har lidt neurologisk skade [11]. MRS måler graden af funktionsnedsættelse samt evnen til at udføre daglige aktiviteter for patienter, der har lidt en neurologisk skade. MRS går fra: 0 (ingen symptomer), 1 (ingen signifikant funktionsnedsættelse), 2 (svag funktionsnedsættelse), 3 (moderat funktionsnedsættelse, 4 (moderat til svær funktionsnedsættelse), 5 (svær funktionsnedsættelse) til 6 (død). Nytteværdien af at gå fra én score til den næste er ikke ens, da der er tale om meget forskellige funktionsniveauer, hvorfor det er vanskeligt at definere en gennemsnitlig ændring, der er klinisk relevant på tværs af skalaen. En opgørelse af patienter med intrakranielle blødninger i AK-behandling fandt, at 36 % af alle og 62 % af de overlevende havde en MRS $\leq$ 2 ved udskrivelse [12].

Der er ikke en standarddefinition for afgræsningen af, hvad der er en god eller dårlig score på MRS for patienter med intrakranielle blødninger. Fagudvalget ønsker at belyse effektmålet som andelen af patienter, der opnår et "godt helbredsstadie", hvilket anses som en MRS-score på mellem 0 og 2. Øvrige scores mellem 3 og 6 betragtes som "uønskede helbredsstadier". Effektmålet ønskes målt 30 dage fra randomisering eller opstart af behandling. Den mindste klinisk relevante forskel fastsættes af fagudvalget til 4 %-point.

5.3.3 Bivirkningsprofil og sikkerhedsaspekter

Fagudvalget lægger vægt på, at der er tale om behandling af en akut livstruende tilstand. Derfor er det også begrænset, hvilke bivirkninger der tillægges vægt i den akutte livstruende situation. Det vurderes dog, at det er nødvendigt at vurdere, hvorvidt der er balance mellem behandlingseffekten (hæmostasekontrol) og den øgede risiko for tromboemboliske hændelser, da denne balance, eller forskydning i balance, mere direkte kan relateres til lægemidlets potentielle effekt.

Tromboemboliske hændelser

Patienter med alvorlige blødninger vil grundet deres underliggende sygdom og reverteringsbehandling, der fjerner den beskyttende antitrombotiske effekt, have en øget risiko for tromboemboliske hændelser. Hos patienter behandlet med PKK er hændelsesraten for tromboemboliske hændelser lav og er rapporteret til ca. 3 % i 5 observationelle studier med 30 dages opfølgningstid [8]. Effektmålet er medtaget, fordi fagudvalget ønsker at sikre sig, at der ikke er tegn på øget risiko for tromboemboliske hændelser.

Det er især andexanet alfas mulige interaktion med TFPI, der begrunder fagudvalgets fokus på tegn på protrombotisk effekt [9]. Fagudvalget ønsker derfor, at ansøger bidrager med en uddybende liste over tromboemboliske hændelser, f.eks. type, placering, dødelighed og gennemsnitlig tid fra opstart af behandling med andexanet alfa/PKK til eventuelle hændelser indtræffer. Fagudvalget ønsker derudover at opgøre effektmålet som forskel i andel patienter, der oplever en tromboembolisk hændelse indenfor 30 dage. Som supplerende oplysning ønsker fagudvalget information om, hvornår og hvor mange af patienterne der genopstarter AK-behandlingen, efter blødningen er stoppet. Dette skal belyse, hvorvidt eventuelle forskelle i tromboemboliske hændelser skyldes forskel i AK-behandlingen eller er lægemiddelrelateret. Fagudvalget forventer som udgangspunkt ikke, at det vil være muligt at detektere nogen forskel mellem grupperne på baggrund af den lave hændelsesrate og studiernes størrelse, hvorfor der ikke defineres en mindste klinisk relevant forskel. Effektmålet vil blive beskrevet narrativt ved at se på al relevant information omkring tromboemboliske hændelser.

Kvalitativ gennemgang

Fagudvalget ønsker at foretage en kvalitativ gennemgang af hændelsestyperne med udgangspunkt i SAE-lister fra studier med henblik på at vurdere, om der er forskel i bivirkningsprofilerne mht. alvorlighed, håndterbarhed og hyppighed af bivirkningerne. Den kvalitative gennemgang af hændelserne vil ligeledes belyse, hvorvidt en eventuel forskel mellem behandlingerne i andel af patienter, der oplever alvorlige hændelser, skyldes klinisk betydende hændelser. Fagudvalget vil inddrage produktresuméerne og EPAR i det omfang, det er nødvendigt.

Den kvalitative gennemgang vil indgå som en overvejelse i den samlede vurdering af lægemidlets værdi.

5.4 Vigtigt effektmål

5.4.1 Hæmostasekontrol (kun for patienter uden intrakranielle blødninger)

Effektmålet skal afdække den hæmostatiske effekt af lægemidlet (farmakologiske effekt). Der findes et bredt spektrum af definitioner for hæmostasekontrol, hvilket medfører, at studier opgør denne parameter på forskellig vis. Den store diversitet vanskeliggør sammenligninger på tværs af studier. Nogle måder at opgøre hæmostasekontrol på anses som tvivlsomt korreleret med kliniske effektmål. *International Society on Thrombosis and Haemostasis* (ISTH) har lavet en ny standardisering med stringente kriterier i forhold til at opnå konsensus omkring bedømmelse af, hvorvidt hæmostasekontrol er opnået og anses som den bedste måde at opgøre hæmostasekontrol på [13]. For at opnå en utvetydig konklusion er ISTH-kriterierne binære;

enten opnås effektiv eller ineffektiv hæmostasekontrol vurderet efter 48 timer. ISTH har opstillet forskellige bedømmelseskriterier for hæmostasekontrol, der afhænger af blødningstype, f.eks. muskuloskeletale blødninger.

Det er uklart, i hvilken grad hæmostasekontrol (bestemt ud fra ISTH) korrelerer med kliniske effektmål som dødelighed og funktionsniveau. For patienter behandlet med PKK opnås hæmostasekontrol, jf. ISTH-kriterier, for ca. 70 % af patienterne [8]. Det forventes, at der vil være nogen diskrepans mellem at opnå effektiv hæmostase og de kliniske relevante effektmål. Som eksempel får patienter med intrakranielle blødninger ofte vedvarende neurologiske skader og funktionsnedsættelse, og dette undgås ikke nødvendigvis ved hæmostasekontrol, da skaden allerede er sket, og det i høj grad er blødningens lokation, der er bestemmende for patientens prognose. Fagudvalget finder derfor, at effektmålet er mindre værdifuldt i forhold til patienter med intrakranielle blødninger. Derimod vil der formentligt være en bedre korrelation for effektmålet hæmostasekontrol og de kliniske relevante hændelser for patienter, der f.eks. har gastro-intestinale blødninger, hvor patienter enten overlever blødningen og sjældent får komplikationer, eller blødningen ikke kan stoppes, og patienten derfor dør.

Fagudvalget finder effektmålet vigtigt for vurderingen ved andre blødninger end intrakranielle blødninger. Fagudvalget finder, at effektmålet kan bidrage med relevant information, der ikke opfanges af de øvrige effektmål hos disse patienter. Fagudvalget finder hæmostasekontrol interessant, da manglende hæmostasekontrol leder til mere understøttende behandling, herunder et større forbrug af blodproduktioner og længere indlæggelse (og er således at opfatte som et surrogat effektmål for sygeligheden i efterforløbet af blødning). Fagudvalget ønsker derfor, at ansøger opgør effektmålet som forskel i andel patienter, der opnår effektiv hæmostasekontrol, jf. ISTH-kriterierne, og den mindste kliniske relevante forskel fastsættes af fagudvalget til 5 %-point.

5.4.2 Livskvalitet

Da der er tale om en akut livstruende situation, vurderes det ikke hensigtsmæssigt eller muligt at vurdere livskvalitet i det akutte forløb. For en væsentlig andel af patienterne kan deres blødninger dog give langsigtede komplikationer og funktionsnedsættelse, der kan have indflydelse på livskvaliteten. Det vurderes derfor vigtigt at vurdere, hvordan de patienter, der overlever, oplever deres livskvalitet efter udskrivning fra hospitalet.

EQ-5D-spørgeskemaet er et velvalideret generisk spørgeskema, som anvendes til vurdering af helbreds-relateret livskvalitet (EuroQol Group). Spørgeskemaet består af fem dimensioner (bevægelighed, personlig pleje, sædvanlige aktiviteter, smerte/ubehag og angst/depression). EQ-5D index scoren går fra 0-1, hvor 1 er det bedst tænkelige helbred. Spørgeskemaet indeholder desuden en visuel analog skala (VAS), der går fra 0 (værst tænkelige helbred) til 100 (bedst tænkelige helbred). Den mindste klinisk relevante forskel er rapporteret på tværs af adskillige studier og forskellige sygdomme. For patienter med apopleksi er den rapporteret til 0,1 i EQ-5D index score [14]. Da en stor del af studiepopulationen forventes at være patienter med intrakranielle blødninger, læner fagudvalget sig op ad denne definition og betragter en forskel på ≥ 0,1 i EQ-5D index score som en klinisk relevant forskel. Fagudvalget vurderer, at effektmålet *livskvalitet* skal opgøres på dag 30 og 180 ift. udskrivning fra hospital.

6 Litteratursøgning

Vurderingen af klinisk værdi baseres som udgangspunkt på data fra peer-reviewed publicerede fuldtekst-artikler og data fra EMAs EPAR – public assessment report(s). Data skal derudover stemme overens med protokollens beskrivelser.

Sekretariatet har på baggrund af den foreløbige ansøgning undersøgt, om der findes et eller flere peer reviewede publicerede fuldtekstartikler, hvor andexanet alfa er sammenlignet direkte med komparator, jf. afsnit 5.1.

Sekretariatet har ikke fundet artikler, som kan anvendes til direkte sammenligning af andexanet alfa og komparator.

Virksomheden skal derfor søge efter studier, der kan anvendes til en indirekte sammenligning af andexanet alfa og komparator. Til det formål har sekretariatet udarbejdet søgestrenge, som skal anvendes i MEDLINE (via PubMed) og CENTRAL (via Cochrane Library). Søgestrengene kan findes i bilag 1. Derudover skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparator(er).

Kriterier for udvælgelse af litteratur
Virksomheden skal først ekskludere artikler på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå med forfatter, årstal og titel i en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et PRISMA-flowdiagram (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal der anvendes et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen vurderes.

Eksklusionskriterier: Kliniske studier med andre populationer end de valgte samt studier, som ikke rapporterer mindst et af de kritiske eller vigtige effektmål, ekskluderes

7 Databehandling og analyse

De inkluderede studier og baselinekarakteristikken af studiepopulationerne beskrives i Medicinrådets ansøgningsskema. Det skal angives, hvilke studier der benyttes til at besvare hvilke kliniske spørgsmål.

Al relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. Der skal udføres en komparativ analyse for hvert enkelt effektmål på baggrund af relevant data fra inkluderede studier. For hvert effektmål og studie angives analysepopulation (f.eks. intention to treat (ITT), per-protocol) samt metode. Resultater for ITT-populationen skal angives, hvis muligt, hvis de primære komparative analyser ikke er baseret på denne population. Alle ekstraherede data skal krydstjekkes med de resultater, der beskrives i EPAR'en. Findes uoverensstemmelser, gives en mulig grund herfor.

Hvis ekstraherede data afviger fra de forhåndsdefinerede PICO-beskrivelser, specielt i forhold til præspecificeret population og effektmål, begrundes dette.

Hvis data for et effektmål ikke er tilgængelig for alle deltagere i et studie, vil der ikke blive gjort forsøg på at erstatte manglende data med en meningsfuld værdi. Det vil sige, at alle analyser udelukkende baseres på tilgængelige data på individniveau.

For effektmål (ORR, SAE, behandlingsstop pga. bivirkninger og ikkealvorlige bivirkninger), hvor det er naturligt at beregne både absolut og relativ forskel, vil den relative forskel være basis for statistiske analyser. Den absolutte forskel vil derefter blive beregnet, baseret på den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen. Det antagne niveau vil afspejle det forventede niveau i Danmark ved behandling med komparator (hvis relativ risiko (RR) = 0,5 og antaget andel med hændelse i komparatorgruppen er 30 %, da er den absolutte risikoreduktion (ARR) = 30 – 30 x 0,5 = 15 %-point).

Hvis der er mere end ét sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans.

For effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, vil eventuelle metaanalyser blive baseret på standardized mean difference (SMD). Den estimerede SMD vil blive omregnet til den foretrukne skala for effektmålet. Til dette formål anvendes medianen af de observerede standard-afvigelser i de inkluderede studier.

Hvis det ikke er en mulighed at udarbejde metaanalyser (herunder netværksmetaanalyser), syntetiseres data narrativt. Studie- og patientkarakteristika samt resultater fra de inkluderede studier beskrives narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er). Forskelle i patientkarakteristika og studiekontekst (f.eks. geografi og årstal) mellem studier skal beskrives og vurderes for at afgøre, hvorvidt resultaterne er sammenlignelige.

Valget af syntesemetode (metaanalyse eller narrativ beskrivelse) begrundes, og specifikke analysevalg truffet i forhold til metoden skal fremgå tydeligt.

8 Andre overvejelser

Fagudvalget ønsker en redegørelse fra ansøger vedrørende den mulige protrombotiske effekt af andexanet alfa. Ansøger bedes med udgangspunkt i præklinisk samt klinisk data belyse karakteren af andexanet alfas interaktion med TFPI og relatere det til, hvorvidt der er observeret hændelser i studierne, der kan indikere en protrombotisk effekt.

Ansøger bedes kommentere på, hvilke overvejelser der ligger bag, at ANNEXA-4-studiet primært rekrutterede patienter med intrakranielle blødninger. Herunder årsag til ændring af protokollen under studiet, således at studiet blev beriget med disse patienter samt årsagen til, at det igangværende prospektive randomiserede open-label-forsøg (NCT03661528) kun rekrutterer patienter med intrakranielle blødninger. Herudover bedes ansøger redegøre for sine eksklusions- og inklusionskriterier med fokus på, hvorvidt der er patienter omfattet af indikationen af lægemidlet, som ikke er undersøgt i studierne.

Fagudvalget ønsker effektestimater for effektmålet dødelighed for intrakranielle blødninger samt andre typer af blødninger opgjort separat for at vurdere, hvorvidt der er heterogenitet i effekten af andexanet alfa.

Fagudvalget ønsker en redegørelse for virkningsvarigheden, herunder behovet for yderligere understøttende behandling ved brug af andexanet alfa.

Fagudvalget er opmærksomt på, at der er stor sandsynlighed for indikationsskred, hvis andexanet alfa anbefales. Fagudvalget vil derfor i vurderingsrapporten kort opsummere, hvilke muligheder der er for indikationsskred samt eventuelle opmærksomhedspunkter.

Fagudvalget ønsker et estimat af præparationstiden for andexanet alfa for at belyse eventuelt lavpraktiske problemer, der kan opstå i den akutte situation.

9 Referencer

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende behandling og forebyggelse af venøse blodpropper hos kræftpatienter

Formand	**Indstillet af**
Pernille Just Vinholt Overlæge, ph.d.	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Udpegning i gang	Region Nordjylland
Kan ikke opfylde Medicinrådets habilitetskrav	Region Midtjylland
Lennart Friis-Hansen Overlæge	Region Syddanmark
Jytte Jensen Overlæge	Region Sjælland
Jesper Kærgaard Overlæge	Region Hovedstaden
Christina Ruhlmann Afdelingslæge, ph.d.	Dansk Selskab for Klinisk Onkologi
Maja Hellfritzsch Poulsen 1. reservelæge, ph.d.	Dansk Selskab for Klinisk Farmakologi
Eva Leinø Overlæge	Dansk Hæmatologisk Selskab
Dorte Gijsbrechts Husum Overlæge, ph.d.	Dansk Cardiologisk Selskab
Anne-Mette Hvas Professor, overlæge	Dansk Selskab for Klinisk Biokemi
Morten Schnack Rasmussen Overlæge	Dansk Selskab for Trombose og Hæmostase
Gillian Dianna Godette Patient/patientrepræsentant	Danske Patienter
Merete Schmiegelow Patient/patientrepræsentant	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. th. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe: Thomas Linemann (projekt- og metodeansvarlig) Snezana Djurisic (projektdeltager)

Anette Pultera Nielsen (fagudvalgskoordinator) Jan-Odgaard Jensen (biostatistiker) Bettina Fabricius Christensen (informationsspecialist) Annemette Anker Nielsen (teamleder)

11 Bilag 1 – Søgeprotokol

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/advanced

#	Søgetermer	Kommentar
1	apixaban[Supplementary Concept]	Søgetermer for DOACs/NOACs
2	apixaban[Title/Abstract] OR Eliquis*[Title/Abstract] OR BMS-562247[Title/Abstract]	
3	Rivaroxaban[MeSH Terms]	
4	rivaroxaban[Title/Abstract] OR Xarelto*[Title/Abstract] OR BAY 59-7939[Title/Abstract]	
5	edoxaban[Supplementary Concept]	
6	edoxaban[Title/Abstract] OR Savaysa*[Title/Abstract] OR DU-176[Title/Abstract]	
7	Factor Xa Inhibitors[MeSH Terms]	
8	factor Xa inhibitor*[Title/Abstract] OR factor 10a inhibitor*[Title/Abstract] OR oral factor Xa[Title/Abstract]	
9	DOAC*[Title/Abstract] OR direct oral anticoagulant*[Title/Abstract] OR directly acting oral anticoagulant*[Title/Abstract]	
10	NOAC*[Title/Abstract] OR novel oral anticoagulant*[Title/Abstract] OR new oral anticoagulant*[Title/Abstract] OR non-vitamin K antagonist oral anticoagulant*[Title/Abstract]	
11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	
12	PRT064445[Supplemental Concept]	Søgetermer for interventioner
13	andexanet[Title/Abstract] OR Andexxa*[Title/Abstract] OR Ondexxya*[Title/Abstract] OR PRT4445[Title/Abstract] OR PRT064445[Title/Abstract] OR r-antidote[Title/Abstract]	
14	factor IX, factor VII, factor X, prothrombin drug combination[Supplementary Concept]	
15	prothrombin complex concentrates[Supplementary Concept]	
16	PCC*[Title/Abstract] OR prothrombin complex*[Title/Abstract] OR prothrombin concentrate*[Title/Abstract] OR factor IX complex*[Title/Abstract] OR FIX complex*[Title/Abstract]	
17	Autoplex-T*[Title/Abstract] OR Beriplex*[Title/Abstract] OR Kcentra*[tiab] OR Konyne*[Title/Abstract] OR Octaplex*[Title/Abstract] OR PPSB*[Title/Abstract] OR Proplex*[Title/Abstract] OR Prothrombinex*[Title/Abstract] OR Prothromplex*[Title/Abstract]	
18	#12 OR #13 OR #14 OR #15 OR #16 OR #17	
19	#11 AND #18	Kombination af DOACs/NOACs og interventioner
20	case report[Title] OR review[Title] OR meta-analysis[Title]	Eksklusion af irrelevante publikationstyper
21	Case Reports[Publication Type] OR Comment[Publication Type] OR Editorial[Publication Type] OR Guideline[Publication Type] OR Letter[Publication Type] OR News[Publication Type] OR Review[Publication Type] OR Systematic Review[Publication Type] OR Meta-Analysis[Publication Type]	
22	#19 NOT (#20 OR #21)	
23	English[Language]	Afgrænsning på sprog. Linje 24 = endeligt resultat
24	#22 AND #23	

CENTRAL: https://www.cochranelibrary.com/advanced-search/search-manager

#	Søgetermer	Kommentar
1	(apixaban OR Eliquis* OR "BMS 562247"):ti,ab,kw	Søgetermer for DOACs/NOACs
2	(rivaroxaban OR Xarelto* OR "BAY 59 7939"):ti,ab,kw	
3	(edoxaban OR Savaysa* OR "DU-176"):ti,ab,kw	
4	[mh "Factor Xa Inhibitors"] OR "blood clotting factor 10a inhibitor":kw	
5	(("factor Xa" OR "factor 10a") NEAR/1 (inhibitor? OR oral)):ti,ab	
6	(DOAC* OR direct NEXT oral NEXT anticoagulant* OR directly NEXT acting NEXT oral NEXT anticoagulant*):ti,ab	
7	(NOAC* OR novel NEXT oral NEXT anticoagulant* OR new NEXT oral NEXT anticoagulant* OR "non vitamin K antagonist oral" NEXT anticoagulant*):ti,ab	
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	
9	(PRT4445 OR PRT064445 OR andexanet OR Andexxa* OR Ondexxya* OR r-antidote):ti,ab,kw	Søgetermer for interventioner
10	(PCC* OR prothrombin NEXT complex* OR prothrombin NEXT concentrate* OR "factor IX" NEXT complex* OR FIX NEXT complex*):ti,ab,kw	
11	(Autoplex-T* OR Beriplex* OR Kcentra* OR Konyne* OR Octaplex* OR PPSB* OR Proplex* OR Prothrombinex* OR Prothromplex*):ti,ab	
12	#9 OR #10 OR #11	
13	#8 AND #12	Kombination af DOACs/NOACs og interventioner
14	("conference abstract" OR review OR meta-analysis):pt	Eksklusion af irrelevante publikationstyper. Linje 18 = endeligt resultat (afgræns til Trials)
15	("clinicaltrials gov" OR trialsearch):so	
16	NCT*:au	
17	#14 OR #15 OR #16	
18	#13 NOT #17	

12 Versionslog

Version	Dato	Ændring
1.0	7. januar 2020	Godkendt af Medicinrådet.