Clinical trial results:
The effect of exercise on pharmacodynamics and pharmacokinetics of a single dose of unfractionated heparin: A randomized, controlled, cross-over study

Summary

EudraCT number	2023-000150-20
Trial protocol	DK
Global end of trial date	13 February 2024

Results information

Result version number	v1 (current)
This version publication date	17 August 2024
First version publication date	17 August 2024

Trial information

Trial identification

Sponsor protocol code	1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT06174961
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Department of Clinical Pharmacology, Bispebjerg-Frederiksberg Hospital
Sponsor organisation address	Bispebjerg Bakke 23, Copenhagen, Denmark, 2400
Public contact	Department of Clinical Pharmacology, Department of Clinical Pharmacology, Bispebjerg-Frederiksberg Hospital, +45 38635102, kristian.karstoft.01@regionh.dk
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 May 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 February 2024
Global end of trial reached?	Yes
Global end of trial date	13 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of a single exercise session (with both legs) on pharmacodynamics and pharmacokinetics of a single dose of subcutaneously administered unfractionated heparin.

Protection of trial subjects:

WattMAX test: A physical fitness test, where subjects must put in maximum effort. This will cause some degree of breathlessness. No risks are anticipated.

Blood sampling: Will cause minor discomfort in terms of a venous catheter. Theoretically, there is a risk for infections and superficial venous thromboses introduced via the catheter. This risk is minimized by use of aseptic technique and by continuous inflow of saline and. The blood volume collected is so small that it will cause no symptoms.

UFH treatment: Common side effects of UFH treatment include short-lasting increased bleeding tendency, local hematomas and injection site reactions (5). Rarely, UFH leads to thrombocytopenia (heparin induced thrombocytopenia – HIT), and very rarely, these cases are severe due to autoimmunicity leading to thromboembolic complications and massive bleeding tendency (16). The risk of HIT is largest in individuals who get heparins on a regular basis, meaning that the risk in the current study, where subjects will only get four UFH injections in total, is considered to be very small. Subjects will be informed about the risk of HIT and typical signs of this and will be instructed to contact the investigator immediately in case of symptoms on HIT.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	01 September 2023
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	15
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Potential participants were recruited through direct contact, advertising on "www.forskningnu.dk"

Pre-assignment

Screening details:

A medical examination, medical history, blood chemistry screen (hematology incl. coagulation markers, liver and kidney markers (incl. potassium)), and a physical fitness test (WattMAX test) was performed. In addition to this, information about the overall study plan and experimental days was provided to the participant.

Period 1

Period 1 title	No exercise vs Double-legged exercise
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	No exercise

Arm description:

Inactive in supine position for 1 hour after receiving UFH in the non-dominant leg.

Arm type	Active comparator
Investigational medicinal product name	Unfractionated Heparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for cutaneous solution, Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

15.000 IU UFH (Heparin 'LEO', 5000 IE/ml, 5 ml per vial) was injected subcutaneously in the thigh in 3 separate injections (1 ml per injection). All injections of UFH was performed in the non-dominant leg

Arm title	Double-legged exercise

Arm description:

Double-legged exercise for 1 hour after receiving UFH in the non-dominant leg. Exercise was initiated at 40% of WattMax and continously adjusted, aiming for a RPE of 12-13.

Arm type	Experimental
Investigational medicinal product name	Unfractionated Heparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial, Concentrate and solvent for cutaneous solution
Routes of administration	Subcutaneous use

Dosage and administration details:

15.000 IU UFH (Heparin 'LEO', 5000 IE/ml, 5 ml per vial) was injected subcutaneously in the thigh in 3 separate injections (1 ml per injection). All injections of UFH was performed in the non-dominant leg

Number of subjects in period 1	No exercise	Double-legged exercise
Started	7	8
Completed	7	8

Period 2

Period 2 title	Dominant leg vs. Non-dominant leg
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Non-dominant leg

Arm description:

Exercise with non-dominant leg for 1 hour after receiving UFH in the non-dominant leg. Exercise was initiated at 50% of what was performed on the double-legged exercise experimental day and continously adjusted, aiming for a RPE of 12-13. The two experimental days with single-legged exercise interventions was matched with regards to exercise intensity.

Arm type	Experimental
Investigational medicinal product name	Unfractionated Heparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for cutaneous solution, Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

15.000 IU UFH (Heparin 'LEO', 5000 IE/ml, 5 ml per vial) was injected subcutaneously in the thigh in 3 separate injections (1 ml per injection). All injections of UFH was performed in the non-dominant leg

Arm title	Dominant leg

Arm description:

Exercise with dominant leg for 1 hour after receiving UFH in the non-dominant leg. Exercise was initiated at 50% of what was performed on the double-legged exercise experimental day and continously adjusted, aiming for a RPE of 12-13. The two experimental days with single-legged exercise interventions was matched with regards to exercise intensity.

Arm type	Comparative
Investigational medicinal product name	Unfractionated Heparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for cutaneous solution, Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

15.000 IU UFH (Heparin 'LEO', 5000 IE/ml, 5 ml per vial) was injected subcutaneously in the thigh in 3 separate injections (1 ml per injection). All injections of UFH was performed in the non-dominant leg

Number of subjects in period 2	Non-dominant leg	Dominant leg
Started	8	7
Completed	8	7

Baseline characteristics

Reporting groups	
Reporting group title	No exercise vs Double-legged exercise

Reporting group description: -

Reporting group values	No exercise vs Double-legged exercise	Total	
Number of subjects	15	15	
Age categorical			
All participants were between 18 and 50 years old			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	15	15	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	28		
standard deviation	± 4	-	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	15	15	
Height			
Units: centimetre			
arithmetic mean	186		
standard deviation	± 5	-	
Weight			
Units: kilogram(s)			
arithmetic mean	81		
standard deviation	± 8	-	
BMI			
Units: kilogram(s)/square metre			
arithmetic mean	23.4		
standard deviation	± 1.4	-	
Maximal heart rate			
Units: beats per minute (bpm)			
arithmetic mean	185		
standard deviation	± 17	-	
Maximal Watt			
Units: watt			

arithmetic mean	305		
standard deviation	± 36	-	
Average systolic blood pressure Units: mmHg			
arithmetic mean	124		
standard deviation	± 9	-	
Average diastolic blood pressure Units: mmHg			
arithmetic mean	72		
standard deviation	± 8	-	
P-antitrombin Units: kIU/L			
arithmetic mean	1.02		
standard deviation	± 0.08	-	

End points

End points reporting groups

Reporting group title	No exercise
Reporting group description:	
Inactive in supine position for 1 hour after receiving UFH in the non-dominant leg.	
Reporting group title	Double-legged exercise
Reporting group description:	
Double-legged exercise for 1 hour after receiving UFH in the non-dominant leg. Exercise was initiated at 40% of WattMax and continously adjusted, aiming for a RPE of 12-13.	
Reporting group title	Non-dominant leg
Reporting group description:	
Exercise with non-dominant leg for 1 hour after receiving UFH in the non-dominant leg. Exercise was initiated at 50% of what was performed on the double-legged exercise experimental day and continously adjusted, aiming for a RPE of 12-13. The two experimental days with single-legged exercise interventions was matched with regards to exercise intensity.	
Reporting group title	Dominant leg
Reporting group description:	
Exercise with dominant leg for 1 hour after receiving UFH in the non-dominant leg. Exercise was initiated at 50% of what was performed on the double-legged exercise experimental day and continously adjusted, aiming for a RPE of 12-13. The two experimental days with single-legged exercise interventions was matched with regards to exercise intensity.	

Primary: Change in aPTT

End point title	Change in aPTT
End point description:	
Change in aPTT measured as maximum aPTT (during the 8 hours after injection of UFH) minus baseline aPTT.	
End point type	Primary
End point timeframe:	
Change in aPTT measured as maximum aPTT (during the 8 hours after injection of UFH) minus baseline aPTT.	

End point values	No exercise	Double-legged exercise	Non-dominant leg	Dominant leg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	8	7
Units: second				
arithmetic mean (confidence interval 95%)	7.9 (3.5 to 12.3)	8.7 (4.2 to 13.2)	16.5 (5.2 to 27.8)	13.1 (0.3 to 26.0)

Statistical analyses

Statistical analysis title	Paired two tailed t-test
Statistical analysis description:	
A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the	

"exercise with non-dominant leg" intervention.

Comparison groups	No exercise v Double-legged exercise
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[1]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	4.5

Notes:

[1] - A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Statistical analysis title	Paired two tailed t-test

Statistical analysis description:

A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Comparison groups	Non-dominant leg v Dominant leg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[2]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	8.8

Notes:

[2] - A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Secondary: Change in plasma heparin

End point title	Change in plasma heparin

End point description:

Change in plasma heparin measured as maximum aPTT (during the 8 hours after injection of UFH) minus baseline plasma heparin.

End point type	Secondary

End point timeframe:

Change in plasma heparin measured as maximum aPTT (during the 8 hours after injection of UFH) minus baseline plasma heparin.

End point values	No exercise	Double-legged exercise	Non-dominant leg	Dominant leg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	8	7
Units: kIU/L				
arithmetic mean (confidence interval 95%)	0.16 (0.12 to 0.19)	0.18 (0.12 to 0.23)	0.23 (0.15 to 0.31)	0.19 (0.12 to 0.27)

Statistical analyses

Statistical analysis title	Paired two tailed t-test

Statistical analysis description:

A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Comparison groups	Double-legged exercise v No exercise
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[3]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.07

Notes:

[3] - A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Statistical analysis title	Paired two tailed t-test

Statistical analysis description:

A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Comparison groups	Non-dominant leg v Dominant leg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[4]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.31

Notes:

[4] - A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Other pre-specified: Mean incremental aPTT	
End point title	Mean incremental aPTT
End point description:	
Mean incremental aPTT during the entire experimental day (ending 8 hours after UFH injection)	
End point type	Other pre-specified
End point timeframe:	
Mean incremental aPTT during the entire experimental day (ending 8 hours after UFH injection)	

End point values	No exercise	Double-legged exercise	Non-dominant leg	Dominant leg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	8	7
Units: second				
arithmetic mean (confidence interval 95%)	2.1 (-1.6 to 5.8)	1.3 (-1.3 to 3.9)	6.4 (-0.1 to 12.8)	4.5 (-2.8 to 11.8)

Statistical analyses

Statistical analysis title	Paired two tailed t-test
Statistical analysis description:	
A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.	
Comparison groups	No exercise v Double-legged exercise
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[5]
Method	t-test, 2-sided
Parameter estimate	Median difference (final values)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	2.3

Notes:

[5] - A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Statistical analysis title	Paired two tailed t-test
Statistical analysis description:	
A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.	

Comparison groups	Non-dominant leg v Dominant leg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[6]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	12.8

Notes:

[6] - A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Other pre-specified: Mean incremental plasma heparin

End point title	Mean incremental plasma heparin

End point description:

Mean incremental plasma heparin during the entire experimental day (ending 8 hours after UFH injection)

End point type	Other pre-specified

End point timeframe:

Mean incremental plasma heparin during the entire experimental day (ending 8 hours after UFH injection)

End point values	No exercise	Double-legged exercise	Non-dominant leg	Dominant leg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	8	7
Units: kIU/L				
arithmetic mean (confidence interval 95%)	0.11 (0.07 to 0.14)	0.11 (0.07 to 0.15)	0.14 (0.09 to 0.20)	0.13 (0.07 to 0.19)

Statistical analyses

Statistical analysis title	Paired two tailed t-test

Statistical analysis description:

A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Comparison groups	No exercise v Double-legged exercise

Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[7]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.03

Notes:

[7] - A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Statistical analysis title	Paired two tailed t-test

Statistical analysis description:

A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Comparison groups	Non-dominant leg v Dominant leg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[8]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.03

Notes:

[8] - A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Other pre-specified: Change in aPTT at t240

End point title	Change in aPTT at t240

End point description:

apTT level 240 minutes after UFH injection minus apTT level at baseline

End point type	Other pre-specified

End point timeframe:

apTT level 240 minutes after UFH injection minus apTT level at baseline

End point values	No exercise	Double-legged exercise	Non-dominant leg	Dominant leg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	8	7
Units: second				
arithmetic mean (confidence interval 95%)	4.6 (-0.6 to 9.9)	3.8 (0.4 to 7.1)	13.1 (3.0 to 23.2)	10.9 (-2.5 to 24.2)

Statistical analyses

Statistical analysis title	Paired two tailed t-test

Statistical analysis description:

A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Comparison groups	No exercise v Double-legged exercise
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[9]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	4.4

Notes:

[9] - A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Statistical analysis title	Paired two tailed t-test

Statistical analysis description:

A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Comparison groups	Non-dominant leg v Dominant leg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[10]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	8

Notes:

[10] - A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Other pre-specified: Change in plasma heparin at t240	
End point title	Change in plasma heparin at t240
End point description:	
plasma heparin level 240 minutes after UFH injection minus plasma heparin level at baseline	
End point type	Other pre-specified
End point timeframe:	
plasma heparin level 240 minutes after UFH injection minus plasma heparin level at baseline	

End point values	No exercise	Double-legged exercise	Non-dominant leg	Dominant leg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	8	7
Units: kIU/L				
arithmetic mean (confidence interval 95%)	0.13 (0.09 to 0.17)	0.13 (0.08 to 0.17)	0.18 (0.10 to 0.26)	0.18 (0.09 to 0.26)

Statistical analyses

Statistical analysis title	Paired two tailed t-test
Statistical analysis description:	
A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.	
Comparison groups	No exercise v Double-legged exercise
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[11]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.04

Notes:

[11] - A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Statistical analysis title	Paired two tailed t-test

Statistical analysis description:

A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Comparison groups	Non-dominant leg v Dominant leg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[12]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.07

Notes:

[12] - A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Post-hoc: Change in aPTT at t60

End point title	Change in aPTT at t60

End point description:

aPTT level 60 minutes after UFH injection minus plasma aPTT level at baseline

End point type	Post-hoc

End point timeframe:

aPTT level 60 minutes after UFH injection minus plasma aPTT level at baseline

End point values	No exercise	Double-legged exercise	Non-dominant leg	Dominant leg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	8	7
Units: second				
arithmetic mean (confidence interval 95%)	1.9 (-0.5 to 4.4)	5.0 (0.3 to 9.8)	6.7 (-0.8 to 14.3)	-3.0 (-5.1 to 0.8)

Statistical analyses

Statistical analysis title	Paired two tailed t-test

Statistical analysis description:

A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Comparison groups	No exercise v Double-legged exercise
Number of subjects included in analysis	15
Analysis specification	Post-hoc
Analysis type	other[13]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	3.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	6.2

Notes:

[13] - A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Statistical analysis title	Paired two tailed t-test

Statistical analysis description:

A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Comparison groups	Non-dominant leg v Dominant leg
Number of subjects included in analysis	15
Analysis specification	Post-hoc
Analysis type	other[14]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	9.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.9
upper limit	15.5

Notes:

[14] - A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Post-hoc: Change in plasma heparin at t60

End point title	Change in plasma heparin at t60

End point description:

plasma heparin level 60 minutes after UFH injection minus plasma heparin level at baseline

End point type	Post-hoc

End point timeframe:

plasma heparin level 60 minutes after UFH injection minus plasma heparin level at baseline

End point values	No exercise	Double-legged exercise	Non-dominant leg	Dominant leg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	8	7
Units: kIU/L				
arithmetic mean (confidence interval 95%)	0.08 (0.06 to 0.10)	0.15 (0.09 to 0.21)	0.16 (0.09 to 0.23)	0.05 (0.03 to 0.08)

Statistical analyses

Statistical analysis title	Paired two tailed t-test

Statistical analysis description:

A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Comparison groups	No exercise v Double-legged exercise
Number of subjects included in analysis	15
Analysis specification	Post-hoc
Analysis type	other[15]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.13

Notes:

[15] - A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Statistical analysis title	Paired two tailed t-test

Statistical analysis description:

A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Comparison groups	Non-dominant leg v Dominant leg
Number of subjects included in analysis	15
Analysis specification	Post-hoc
Analysis type	other[16]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.16

Notes:

[16] - A paired two tailed t-test was conducted. The "No exercise" intervention was compared to the "double-legged exercise" intervention, while the "exercise with dominant-leg" intervention was compared to the "exercise with non-dominant leg" intervention.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs are registered in the electronic CRF at the end of the intervention days and one week after each intervention day.

Assessment type	Systematic

Dictionary used

Dictionary name	ICH GCP
Dictionary version	R1

Reporting groups

Reporting group title	All participants

Reporting group description: -

Serious adverse events	All participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	All participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 15 (33.33%)		
Vascular disorders			
Syncope	Additional description: One individual had a vasovagal syncope and fainted in relation to his venous catheter being adjusted		
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Haematoma	Additional description: One individual experienced a hematoma in relation to where his venous catheter had been located		
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Muscle discomfort	Additional description: 3 individuals experienced mild muscle soreness in relation to experimental days involving exercise		

subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported