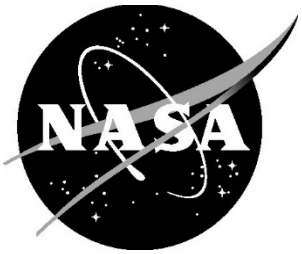
NASA/Special Publication – NASA/SP-20250001074/REV1



Assessment of Risk of Venous Thromboembolism during Spaceflight

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This revised copy, numbered as NASA/SP-20250001074/REV1, March 2025, supersedes the previous version, NASA/ SP-20250001074, January 2025, in its entirety.

DOCUMENT HISTORY LOG

Status	Document Revision	Approval Date	Description
Baseline		2025-01-28	Initial Release
Revision	REV1		Partial revision with the following major changes: Added "unprovoked" to p. 14: "A history of unprovoked venous thrombosis in immediate family members is considered a risk factor for VTE…" Added data on hormone use among female long duration crewmembers who flew on ISS expeditions of at least 6 months on p. 16. Replaced Hormone Comparison Table on p. 18 with new version with sources cited in place of websites and a key to define color coding. Changed dosing recommendation for Apixiban initial dose from "10 mg twice a day initial dose (5-10 days); afterwards 5 mg twice a day" to "Apixaban 10 mg twice a day for 7 days; afterwards 5 mg twice a day" on p. 26. Added hormone use to risks described under the subheading "In-flight Ultrasound Assessment – No Thrombosis Discovered" on p. 26. Replaced flow diagram on p. 28 to update Apixiban dose and add Hormone Use to decision block along with Thrombophilia and Family History. Added note: **Unprovoked thrombosis in immediate family members; hormones that increase the risk of VTE (see Hormone Comparison Table on p. 18)

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NASA STI Program / Mail Stop 050

NASA Langley Research Center

Hampton, VA 23681-2199

Risk of Venous Thromboembolism during Spaceflight

Introduction

NASA's Office of the Chief Health and Medical Officer (OCHMO) initiated a working group to review the status and progress of research and clinical activities intended to mitigate the risk of venous thromboembolism during spaceflight. The working group took place over two days at NASA's Johnson Space Center in October 2024.

NASA Presenters

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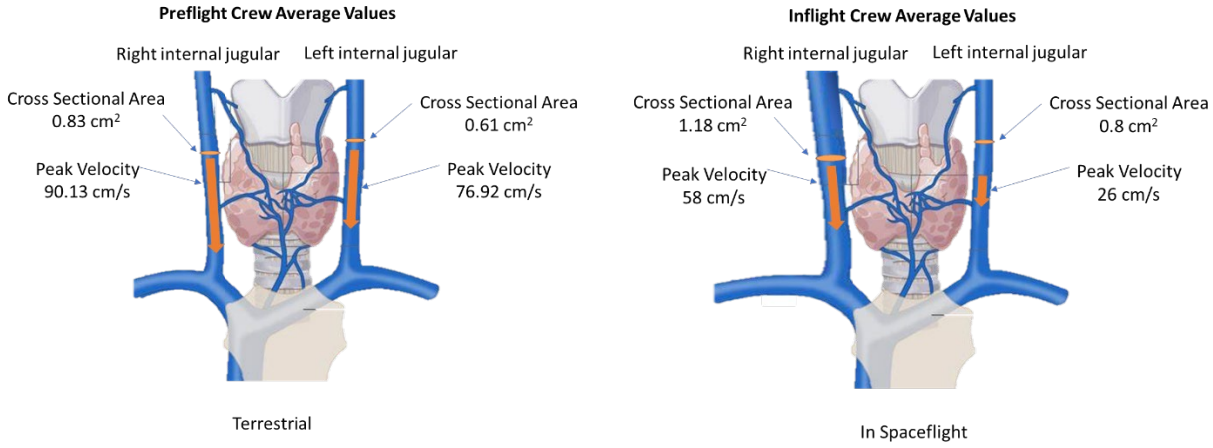
Background

Spaceflight Venous Thrombosis (SVT)

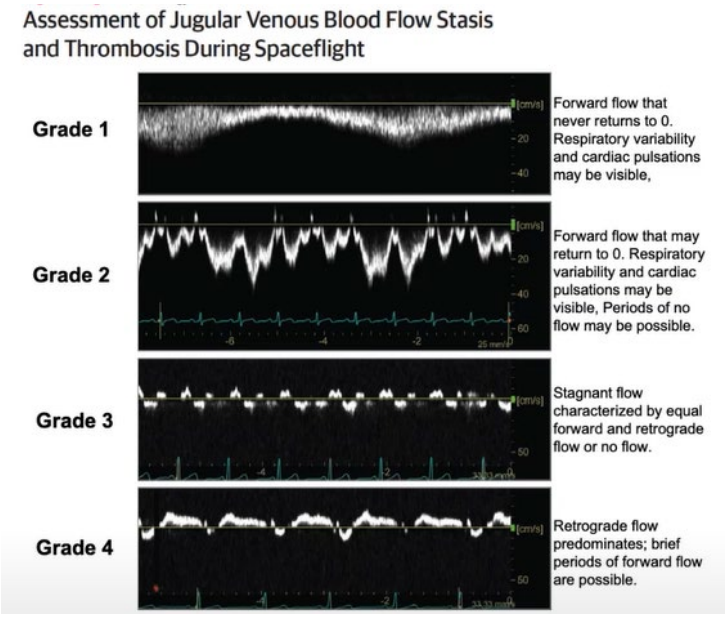
Spaceflight Venous Thrombosis (SVT) refers to a phenomenon experienced during spaceflight in which a thrombus forms in the internal jugular vein (and/or associated vasculature) that may be symptomatic (thrombus accompanied by, but not limited to, visible internal jugular vein swelling, facial edema beyond "nominal" spaceflight adaptation, eyelid edema, and/or headache) or asymptomatic.

Altered blood flow has been observed in both the left and right internal jugular veins concomitant with vessel distension. Flow in the left jugular vein may be antegrade but with the flow lower than terrestrial norm, stasis, and/or retrograde flow. The left and right internal jugular veins usually increase in cross sectional area in microgravity, compared to terrestrial settings.



Averaged crew (11 crewmembers) preflight and in-flight cross-sectional area and peak velocity of the internal jugular vein.
Source: NASA occupational surveillance, Presented at VTE Working Group October 2024

Some crewmembers have experienced stasis and retrograde flow in the left internal jugular vein but not the right. A grading system was developed to classify the flow and is shown in the following ultrasound graphic.



In-flight ultrasound images and flow grading.
Source: Marshall-Goebel et al., 2019

Preliminary data from 22 crewmembers are presented in the table below. Approximately 54% are experiencing stasis/stagnant flow (grade 3) or retrograde flow (grade 4). The right internal jugular was consistently classified as a Grade 2 – antegrade/ forward flow.

Left IJV

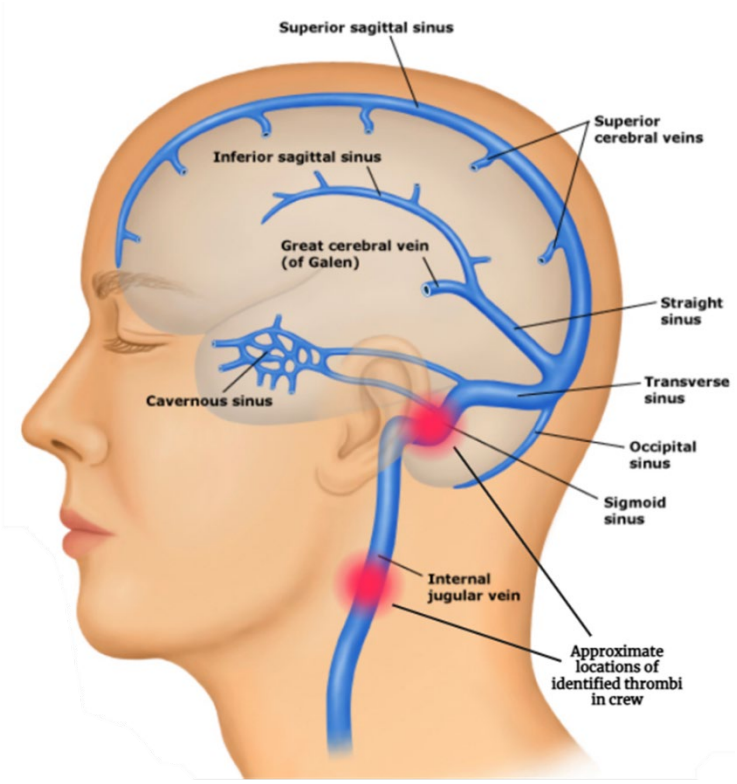
Subject	Preflight (Supine)	Inflight	
		FD50	FD150
1	1	2	4
Adapted	2	2	2
3	2	3	3
4	2	2	2
5	2	3	2
6	2	3	3
7	2	3	-
8	2	4	2
9	2	3	2
10	2	2	2
11	2	1	2

Left IJV

Subject	Preflight (Supine)	Inflight		
		FD30	FD60	FD168
A	2	3	3	3
B	2	2	2	2
C	1	2	3	4
D	2	2	-	-
E	2	2	2	2
F	2	3	2	3
G	2	2	2	2
H	2	2	2	2
I	2	1	2	2
J	2	2	2	2
K	-	2	2	2

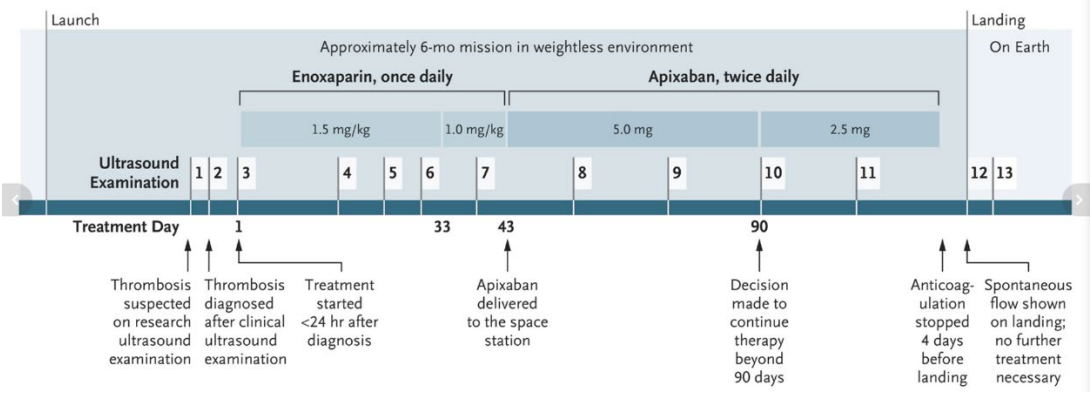
Data from two studies depicting in-flight grading of ultrasound images of the IJV.
Source: Marshall-Goebel et al., 2019

Obstructive thrombi have been identified in a very small number of crewmembers.



Note: For illustrative purposes only; locations are approximate, and size is not to scale.
Source: Modified from Cerebral Sinus Venous Thrombosis – University of Colorado Denver, n.d.

After diagnosis with ultrasound in-flight, crew have been treated as per the following regimen:



Example treatment regimen. Treatment must be tailored to an individual's circumstances, such as interpretation of venous Doppler ultrasound findings, symptoms, bleeding risk, etc.
Source: Aunon-Chancellor et al., 2020

With treatment, crewmembers were able to complete their mission and prior to landing, anticoagulants were discontinued several days prior to return to Earth to minimize the risk of bleeding in the event of a traumatic injury. Some thromboses completely resolved post landing, and some required additional treatment.

Working Group Formation

The purpose of this working group was to review and provide analysis on the status and progress of research and clinical activities intended to mitigate the risk of VTE during spaceflight. The working group was assembled from internal NASA subject matter experts, the NASA OCHMO Standards Team, NASA and ESA stakeholders, and external subject matter experts including experts in cardiology, vascular medicine and hematology, neurology, spaceflight medicine, ophthalmology, and basic coagulation laboratory science. The working group was asked to review past reports and evidence related to VTE, receive materials and information regarding NASA's current observations, experience and practices, present case studies and subsequent decision-making processes, and participate in an open-forum discussion.

Group Charter

Pre-defined goals of the working group included:

Goal 1: Review of the data taken as part of surveillance

Goal 2: Expansion of the current surveillance methods to include biomarkers (e.g., D-Dimer)

Goal 3: Identification of high-risk individuals

Goal 4: Identification of potential countermeasures to prevent incidence of VTE during spaceflight:

1. Identification of customized countermeasures based on individual risk profile
2. Prophylactic use of anti-thrombotics, such as low-dose anti-coagulants
3. Venous flow augmentation with Müller's maneuver and/or threshold impedance devices
4. Fluid shift countermeasures (such as lower body negative pressure and venous occlusive thigh cuffs)

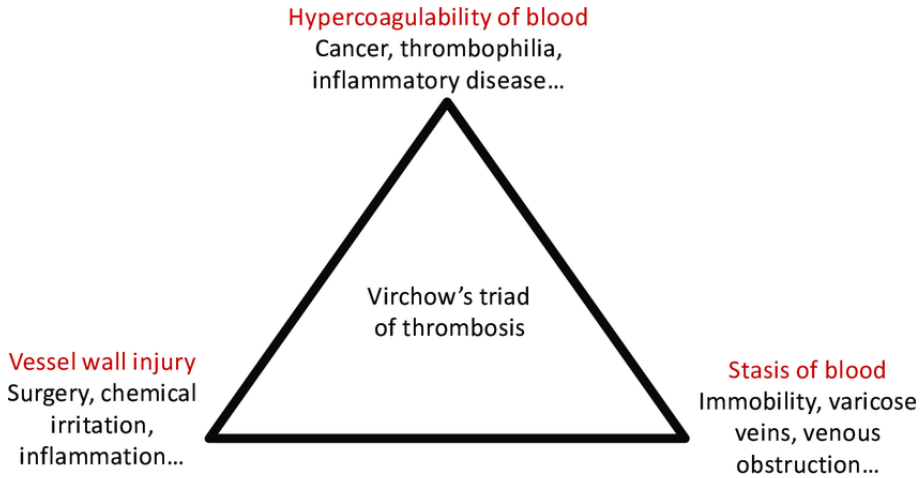
Pathophysiology

The following sections provide the main highlights of feedback and brainstorming from the working group, with additional context and conclusion statements from the meeting as compiled by OCHMO members, Laura L. Bostick, Sarah D. Childress, Kristin M. Coffey, Joanne L. Kaouk, and David R. Francisco, and reviewed by the subject matter expert working group participants.

Pathophysiology of Venous Thromboembolism (VTE)

The proposed pathogenesis of VTE is referred to as Virchow's triad and suggests that VTE occurs as the result of:

a) Alternations in blood flow (i.e., stasis),
b) Vascular endothelial injury/changes, and/or,
c) Alterations in the constituents of the blood leading to hypercoagulability (i.e., hereditary predisposition (Bauer & Lip, 2024) or acquired hypercoagulability.



The Virchow's triad of risk factors for venous thrombosis.
Source: Bouchnita, 2017

Blood stasis, or venous stasis, refers to a condition in which the blood flow in the veins, especially within the legs, slows down which leads to pooling in the veins. This slowing of the blood may be due to vein valves becoming damaged or weak, immobility, and/or the absence of muscular contractions. Associated symptoms include swelling, skin changes, varicose veins, and slow-healing sores or ulcers. In terrestrial medicine, venous thrombosis is typically caused by damaged or weakened vein valves, which can be due to:

- Aging – as people age, valves in the veins become less efficient

- Blood clots – such as a history of DVT, which damages the vein valves
- Varicose veins – which cause valve damage
- Obesity – excessive weight puts pressure on the veins
- Pregnancy – due to increased blood volume causing strain on the veins and valves
- Sedentary lifestyle – sitting or standing for long periods increases risk (Longmore Clinic, 2023)

Mechanisms of vascular endothelial injury include damage to the endothelial walls of the blood vessels. A healthy endothelium has antithrombotic and anti-platelet surfaces. Various pathological processes can cause shedding of the important molecules of the cell surface, leading to an increased risk of pro-coagulation and alterations of blood flow dynamics. Smoking, chronically elevated blood pressure, and atherosclerotic disease are some risk factors that can lead to vascular endothelial injury (Kushner et al., 2024).

Alterations in constituents of the blood that can lead to hypercoagulability include hereditary predispositions, such as the presence of Factor V Leiden, or acquired ones, such as antiphospholipid antibodies or changes induced by hormonal therapy. Additional hereditary and other risk factors of VTE are described in the section titled *Risks to Consider When Assessing VTE in Spaceflight*.

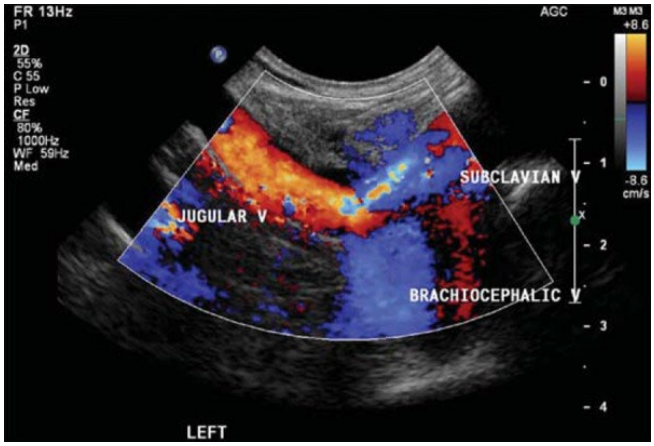
Spaceflight Considerations

In addition to the terrestrial risk factors of VTE, there are physiological changes associated with spaceflight that are hypothesized to potentially play a role in the development of VTE in weightlessness. Specifically, researchers have explored the effects of the microgravity environment and subsequent observed headward fluid shifts that occur, and the potential impact on blood flow (Lawley et al., 2017; Baran et al., 2021). Crewmembers onboard the International Space Station (ISS) experience weightlessness due to the microgravity environment, and thus experience a sustained redistribution of bodily fluids from the legs toward the head. The prolonged headward fluid shifts during weightlessness results in facial puffiness, decreased leg volume, increased cardiac stroke volume, and decreased plasma volume.

Retrograde Venous Blood Flow (RVBF)

Retrograde venous blood flow (RVBF) refers to the backflow of venous blood towards the brain. RVBF can transmit pressure back into the cerebral venous system, causing cerebral venous hypertension (Cheng et al., 2013; Rodrigues et al., 2020). While the etiology of the observed stasis and retrograde blood flow in spaceflight participants is

not well understood, the potential clinical significance of the role it may have in the development of VTE is worth further investigation.



Doppler imaging of a retrograde flow in the left internal jugular vein.
Source: Yan & Seow, 2009

Spaceflight Associated Neuro-ocular Syndrome (SANS)

Other physiological concerns, including Spaceflight Associated Neuro-ocular Syndrome (SANS), which are affected by fluid shifts, are being studied to consider if any relation to VTE exists. SANS refers to a constellation of ocular findings observed in astronauts during and following long-duration spaceflight that can lead to decrements in vision, possibly affecting crew capability and task performance, and the risk of long-term eye health issues. SANS etiology is not certain but fluid shifts resulting in venous congestion and intracranial pressure elevations are considered one of the most likely causes. A significant IJ vein thrombosis could contribute to elevated ICP and impaired cerebral venous drainage, and thus contribute to SANS. Alternatively, SANS and IJ VTE could share a common pathophysiology related to venous congestion. SANS is commonly seen in long-duration crewmembers: 71% of ISS crewmembers have been diagnosed with SANS, while 16% have developed clinically concerning SANS. SANS severity is related to mission duration, making it a significant risk for future long-duration missions such as Mars exploration. Data tying SANS to VTE are currently sparse and inconclusive (NASA HRP, 2022a; NASA HRP, 2022b).

Risks to Consider When Assessing VTE in Spaceflight

When assessing VTE in spaceflight, the following risks should be considered along with ultrasound, physical, and alternative screening assessments.

Family History

A history of unprovoked venous thrombosis in immediate family members is considered a risk factor for VTE, as shown in the following table (Bezemer et al., 2009).

Family History	***Relative Increase in Risk of Thrombosis***
First degree relative with history of VTE < age 50	Up to 2-fold
Multiple first-degree relatives with history of VTE	Up to 4-fold
Family history combined with a genetic or environmental risk (i.e., surgery, injury, immobilization, pregnancy, use of oral contraceptives/hormone therapy, or malignancy)	Up to 64-fold

Relative increase in risk of thrombosis with family history.
Source: Bezemer et al., 2009

Thrombophilias

Thrombophilias include a variety of genetic mutations that are associated with increased risk of VTE. Thrombophilia, either acquired or hereditary, can be identified in approximately 10% of the general population and can be identified in a number of patients presenting with VTE. The currently most commonly tested hereditary thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations Factor V Leiden (FVL) and prothrombin G20210A (PGM) (Albagoush, 2023). The table below shows the relative increase in risk of thrombosis for various thrombophilia conditions.

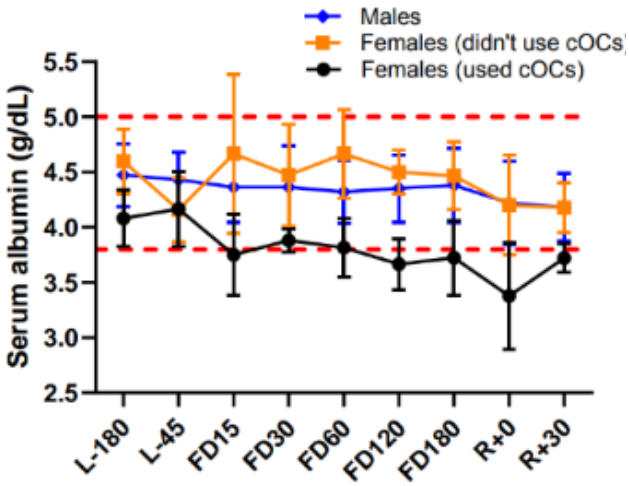
Thrombophilia Condition	***Relative Increase in Risk of Thrombosis***
Factor V Leiden heterozygous	4.9-fold (3-8 fold)
Factor V Leiden homozygous	16-fold
Factor V Leiden with other thrombophilia conditions like a prothrombin gene mutation	20-fold
Protein C deficiency	7-fold
Protein S deficiency	7-fold
Antithrombin III deficiency	16-fold (up to 20-fold)
Prothrombin gene mutation, heterozygous	3.8-fold

Relative increase in risk of thrombosis with various thrombophilia conditions.
Source: Albagoush, 2023

Hormone Therapy

Hormone management or suppression is commonly used by crewmembers, as the logistics of menstruating during spaceflight can be challenging (waste disposal, volume/mass hygiene products) (Jain, 2016). Therapeutic devices (e.g., levonorgestrel intrauterine device [LNG-IUD]), or treatment including combination oral contraceptive (COC) pill, transdermal patches, or depot medroxyprogesterone acetate can all be used to prevent menstrual flow.

Some of these hormones pose a well-established VTE risk (Zwart et al., 2022). COC and estrogen use pose VTE risk concerns: exogenous estrogen when metabolized through the liver produces clotting factors that can increase the thrombotic state (risk varies based on estrogen/progesterone types and concentrations) (Abou-Ismail et al., 2020). Hormones can cause decreased serum albumin associated with hypercoagulability, and damage to the wall of the blood vessel (Harding & Heaton, 2022). These factors all contribute to Virchow's triad (a theory that describes factors that contribute to a thrombosis) increasing the risk of thrombosis and VTE development (Zwart et al., 2022).



Source: Zwart et al., 2022

Currently, crewmembers may be on a variety of hormones (e.g., oral contraceptives to block or regulate menstruation, hormone replacement therapy, etc.) which pose different levels of VTE risk. Second generation COC are the safest combination oral contraceptives, while OC with higher doses of estrogen (50 mcg), either ethinyl estradiol or mestranol, are associated with a significant increase of VTE risk (Morimont et al., 2021); similarly, the progestin preparation plays a role in thrombosis risk, with COC with third generation progestins (desogestrel, gestodene, and norgestimate) and fourth generation progestins (drospirenone, dienogest, nomegestrol acetate, and nestorone) posing a higher risk of VTE than the second generation pills (levonorgestrel) (Hugon-

Rodin et al., 2014; Louw-du Toit, 2016; Sitruk-Ware, 2008; Treger, 2021). Alternative methods to medically induce amenorrhea are available with no or minimal VTE risk such as LNG-IUD, progestin only pills, or the levonorgestrel implant (LaVasseur et al., 2022). One additional factor when considering hormone or OC use is that estrogen inhibits bone resorption through osteoclastic and osteoblast activity and may have protective effects on bone mineral density preservation (Jain, 2016).

Data on female long duration crewmembers who flew on ISS expeditions of at least 6 months are as follows:

- Prior to the first reported VTE case in 2018, 13 female long duration crewmembers flew on ISS expeditions of at least 6 months. The average age at flight was 45.0 years old, and 11 of the 13 female crewmembers were on hormonal oral menstrual suppression medication.
- From 2012 to 2018 (the 6-year period prior to the first reported VTE case), 4 female long duration crewmembers flew on ISS expeditions of at least 6 months, and 3 of the 4 female crewmembers were on hormonal oral menstrual modifying medication.
- From 2018 to 2024 (the 6-year period after the first reported VTE case), 13 female long duration crewmembers flew on ISS expeditions of at least 6 months. The average age at flight was 43.9 years old, and 10 of the 13 female crewmembers were using either hormonal oral menstrual suppression medication or a hormonal intrauterine device with a large majority choosing a hormonal intrauterine device.
- Since the first VTE case, NASA flight surgeons have been prescribing “lower risk” hormone therapy (see Hormone Comparison Table on p. 18).

Martinelli et al. (2016) acknowledge the literature is inconclusive on whether hormone therapy should be discontinued when starting direct oral anticoagulants (DOACs) for prophylactic use or treatment of a thrombus. They state:

> “The World Health Organization (WHO) 2010 guidelines state that use of estrogen-containing contraceptives confers an “unacceptable health risk” during established anticoagulant treatment of VTE (Medical Eligibility Criteria, 2010). By contrast, the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis recommends that women diagnosed with a hormone-associated VTE continue oral contraceptive and estrogen-replacement hormonal therapy until they discontinue anticoagulant therapy (Baglin et al., 2012), because any prothrombotic effect of hormonal therapy is likely to be suppressed by therapeutic-intensity anticoagulation, whereas the risk

> of menorrhagia associated with stopping hormonal therapy could be intensified by anticoagulants (p. 1417)."

Martinelli et al. (2016) used the large EINSTEIN DVT and pulmonary embolism (PE) study cohort to compare the incidences of recurrent VTE and abnormal uterine bleeding in women with and without concomitant hormonal therapy receiving anticoagulant treatment with either rivaroxaban or enoxaparin/VKAs for confirmed symptomatic DVT and/or PE. This analysis of women treated with anticoagulants for acute VTE showed a similar rate of recurrent VTE in those who did and did not receive hormonal therapy (3.7%/year vs. 4.7%/year, respectively). The analysis also showed that abnormal uterine bleeding occurred more frequently with rivaroxaban than with enoxaparin/VKAs (29.8%/year vs. 15.5%/year, respectively).

Based on these findings, it is recommended that crewmembers using a COC should not discontinue use if direct oral anticoagulants (DOACs) are administered to treat a suspected or confirmed thrombus due to the risk of abnormal uterine bleeding (AUB) (Baglin et al., 2012; Martinelli et al., 2016).

Tranexamic acid (TXA) is an antifibrinolytic medication that is used to treat used to control bleeding after trauma as well as to treat heavy bleeding during menstrual period cycles. Tranexamic acid is available for oral administration, and only needs to be taken during the heavy bleeding period of the menstrual cycle. TXA may be an option to help treat increased uterine bleeding that can occur with apixaban use.

Although antifibrinolytics have historically been considered contraindicated in women with a history of thrombosis, large studies of patients at high risk for VTE have failed to demonstrate increased VTE incidence, and no studies have been done on the combination of anticoagulants and antifibrinolytics (Samuelson Bannow, 2020). Dr. Samuelson Bannow goes on to state, "…although use [of TXA] in the immediate post-VTE would be inadvisable because of the desire for ongoing fibrinolysis of the thrombosis, the benefit may outweigh the risks in specific situations, particularly if it enables the continuation of anticoagulants without interruptions" (p. 536). TXA is not currently carried on the ISS, but the committee recommended it be added to the medical kit.

Hormone Comparison Table

Hormone Preparations	Progesterone	Estrogen (mcg)	# of ISS crew	VTE Risk
Progestin only pills	Norethindrone	None		Low/No increased risk[1]
LNG IUD	Drospirenone/ Levonorgestrel	None	6	Low/No increased risk[2]
Implant	Levonorgestrel	None		Low/No increased risk[3]
Hormone Testosterone micronized 2mg	None	None	1	Low/No increased risk
Testosterone Cypionate injections	None	None	1 (male)	Low/No increased risk
Hormone Therapy Estrogen		Estradiol patch	1	Low/No increased risk[1]
		Premarin oral	1	2-fold increase[1]
Progesterone	Micronized progesterone 100mg (Oral)	None		Low/No increased risk[5]
	Medroxyprogesterone depot 150mg	None	2	2.6-fold increase[2]
2nd Generation Progesterone CoC	Levonorgestrel	Ethinyl estradiol (20,10)		2.8-fold increase[4]
		Ethinyl estradiol (20)	2	
		Ethinyl estradiol (30)	1	
		Ethinyl estradiol (20,25,30,10)		
		Ethinyl estradiol (20,10)		
1st Generation Progesterone CoC	Norethindrone acetate	Ethinyl estradiol (10,10)		3.2-fold increase[2]
		Ethinyl estradiol (20)	1	
		Ethinyl estradiol (30)	1	
		Ethinyl estradiol (20,30,35)		
	Norethisterone	-		
	Norethindrone	Ethinyl estradiol (35)	1	
	Ethynodiol diacetate	Ethinyl estradiol (35)		
		Ethinyl estradiol (50)		
	Norgestrel	Ethinyl estradiol (30)	1	
		Ethinyl estradiol (50)		
	Medroxyprogesterone	-		
3rd Generation Progesterone CoC	Norgestimate	Ethinyl estradiol (35)		3.8-fold increase[4]
	Desogestrel	Ethinyl estradiol (20,0,10)		
		Ethinyl estradiol (30)		
	Gestodene	-		
4th Generation Progesterone CoC	Drospirenone	Ethinyl estradiol (30)		Similar to 3rd generation progesterone CoC[1]
		Ethinyl estradiol (30)		
		Estetrol (14.2 mg)		

1. LaVasseur et al., 2022; 2. Cockrum et al., 2022; 3. Perez et al., 1997; 4. Alsheef et al., 2022; 5. Bińkowska, 2014

Key: Low/no increased risk of VTE Some increased risk of VTE Moderate increased risk of VTE

Other Risk Factors for VTE

Many risk factors of VTE (AHA, 2023) are generally not applicable to the astronaut population, including:

- Major surgery or hospitalizations
- Heart conditions, such as heart attack or congestive heart failure
- Chronic conditions including high blood pressure, diabetes, and kidney disease
- Lower-extremity paralysis due to spinal cord injury
- Fracture of the pelvis, hip, or long bones
- Infections, such as the virus that causes COVID-19
- Multiple trauma
- Cancer
- Obesity
- Immobility
- Smoking
- Certain nutritional deficiencies (such as folate or vitamin B12 deficiency)

The working group recommended that the following risk factors for VTE, while applicable to the astronaut population, should not be considered in the development of prophylactic treatment guidelines.

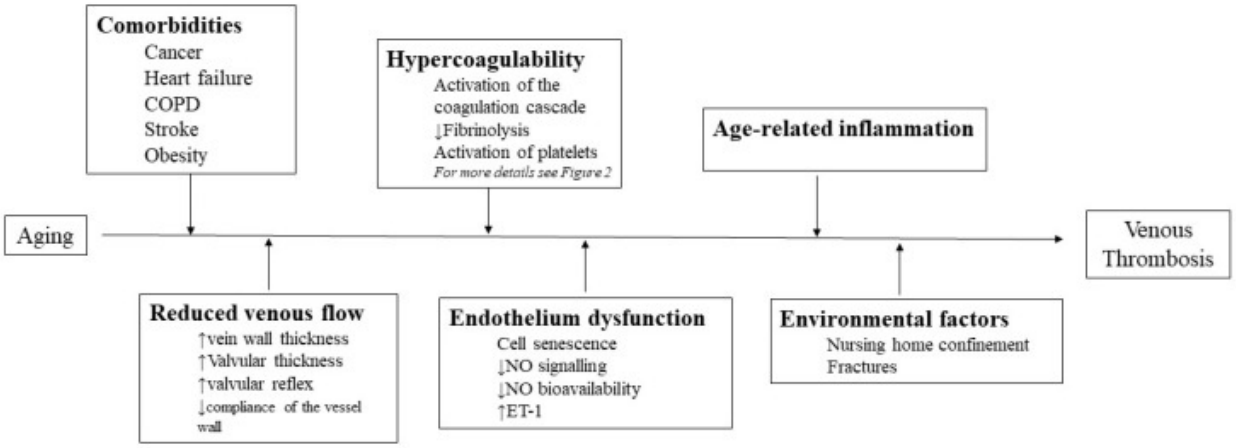
Sex (Male/Female)

Upon literature review, recent publications appear to have conflicting and mixed results regarding sex differences as a VTE risk (Arnesen et al, 2022; Luuk et al., 2022; Melgaard et al., 2019; Naess et al., 2007). With the lack of clarity, it has been concluded that sex differences should not be considered a risk factor for VTE as of now, and further research needs to be conducted. Despite the mixed results, it has been well agreed upon that men with unprovoked VTE have a higher risk of experiencing a recurrent VTE (Douketis et al., 2011).

Age

Increased age is considered a risk factor for thrombosis and aging can be presumed as an acquired thrombophilic state. VTE incidence rates in patients aged ≥65 years are 3-fold higher than in patients aged 45–54 years. Specifically, there is a >7–10-fold increase from ages <55 to >75 years (Akrivou et al., 2022; Cushman et al., 2004). The mechanism underlying this association includes hypercoagulability, endothelial senescence, and venous stasis along with increased chronic inflammation. Additional factors including comorbidities that are commonly present in the elderly (i.e., cancer, chronic heart failure, and stroke) may significantly affect the prothrombotic tendency of older

individuals. All the aforementioned factors are possibly interrelated and result in the increased risk of VTE associated with older age (Akrivou et al., 2022).



The main mechanisms underlying the impact of aging on VTE risk.
↑: up-regulation, ↓: down-regulation.
Source: Akrivou et al., 2022

Due to variances in VTE risk assessment models as to what age should be considered, and the fact that the comorbidities and environmental factors shown in the figure above do not apply to the astronaut population, age was not considered in the development of prophylactic treatment guidelines.

NASA Screening Process

The NASA Space Flight Medical Selection, Recertification and Mission Evaluation Standards document (OCHMO-STD-100.1A) provides medical requirements and clinical procedures designed to ensure crew health and safety and occupational longevity of NASA career astronauts. This NASA Technical Standard is used for selection and annual recertification of astronauts and provides medical evaluation criteria for low-Earth orbit spaceflight missions and is publicly available for viewing online at: *https://www.nasa.gov/wp-content/uploads/2024/09/ochmo-std-100-1a-rev-a-signed.pdf?emrc=9334bc*.

Subsets of screening and testing that may identify risk factors for VTE include:

Laboratory Tests on Selection of NASA Astronauts

- Hematology/Thrombophilia Screen
  - Complete Blood Count – To include hemoglobin, hematocrit, red blood cell count, red blood cell indices, white blood cell count, differential count, platelet count
  - Reticulocyte count

  - Screening tests for thrombophilia: Prothrombin time (PT) and partial thromboplastin time (PTT)
  - Hemoglobin evaluation (A, A2, F, S, C, E)

Astronaut Candidate (ASCAN) First Annual Medical Examination

- Venous Thromboembolism Panel
  - Cardiolipin IgG Antibody
  - B2 glycoprotein 1 IgM/IgG Antibody
  - Activated Protein C (APC) Resistance
  - Prothrombin Nucleotide 20210 G/A Gene Mutation (Factor II)
  - Protein C
  - Protein S
  - Antithrombin
  - Anti-phospholipid antibodies
  - Factor V Leiden

Laboratory Tests on Annual Recertification of NASA Astronauts

- Hematology
  - Complete Blood Count – To include hemoglobin, hematocrit,
  - red blood cell count, red blood cell indices, white blood cell count, differential count, platelet count
  - Reticulocyte count
- Urinalysis
  - Routine (specific gravity, glucose, protein, pH, ketones, blood), microscopic

Specialist Assessments for Selection and Annual Recertification of NASA Astronauts

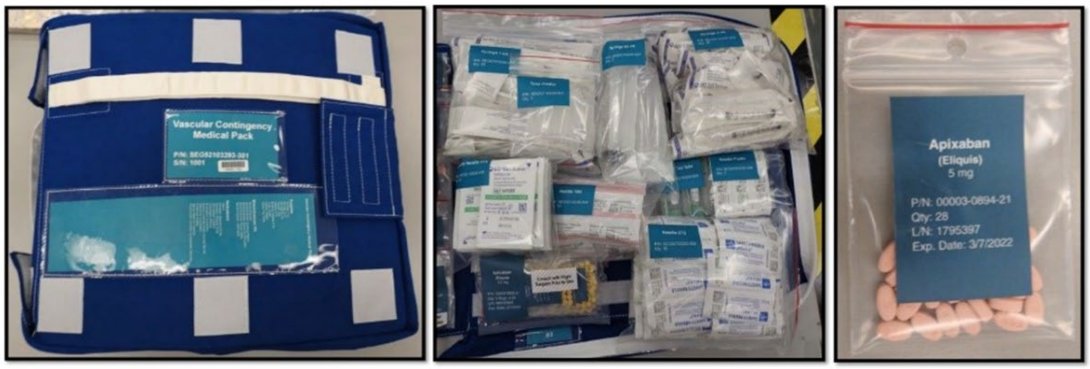
- Neurology
  - MRI of brain
  - MRI angiogram
  - Carotid Ultrasound Study (to include intima medial thickness and/or carotid plaque area)
- Cardiopulmonary
  - Resting 12-lead electrocardiogram (ECG)
  - Direct or indirect measurement of cardiorespiratory fitness (CRF) in ml/kg/min on maximum exercise stress test
  - Echocardiogram, Doppler, and color flow study
  - 24-Hour ECG monitoring
  - Pulmonary function testing
  - Atherosclerotic Cardiovascular Disease Risk Calculation
  - Coronary calcium scoring

Mission Medical Examinations for Assigned Crew on > 30-day Missions

Clinical Assessment and Monitoring	Pre-Flight (L-)	In-Flight	Post-Flight (R+)
Pre- and Post-flight Physical Exam for Short Duration Crews	AME L-12/6 m, L-21/14 d, L-2/1 d		R+0 d and R+3/7 d, PEX ACI - Labs and PEX ID Swab
Ultrasound Imaging (Sonography)	Carotid ultrasound AME 21/18 m unless Within last 5 years, AME L-12/6 m	ACI	ACI
MRI Brain and MR angiography	AME L- 21/18m if > 2 years since selection		ACI
Laboratory Testing	AME L-12/6 m	Blood and urine testing in-flight L+180d and ACI.	Blood and Urine R+0/1, R+3/7, R+14/30
Screening for deep vein thrombosis and venous flow anomalies of the internal jugular veins	L-12/3 m	L+30 days; L+60 days	R-42 days, R+0/45d, ACI

AME = Annual Medical Exam *L +/- = days or months from Launch*
R +/- = days or months from Return to Earth *ACI = As Clinically Indicated*

VTE Treatment Guidelines – Spaceflight and Terrestrial



ISS Vascular Contingency Medical Kit Contents
Source: Pavela, 2024

Kit contains:
Enoxaparin, apixaban, aspirin, metoprolol, and atorvastatin
Reversal agents: 4 factor prothrombin complex concentrate and protamine sulfate
Point-of-care blood analyzer (iStat) with troponin and basic chemistry capability

Treatment Comparison

Currently the ISS medical kit includes anticoagulants enoxaparin (low molecular weight heparin LMWH), apixaban (direct acting oral anticoagulant DOAC), and aspirin. The treatment approach is individualized when considering factors such as patient factors/history (including medication interactions), clinical situation, and

administration/storage capabilities. The current therapy of choice for VTE prevention and treatment on ISS is the DOAC apixaban. Based on existing data, DOACs have similar efficacy but a better safety profile (lower risk of major bleeding) than conventional antithrombotics including aspirin, low molecular weight heparin (LMWH), and warfarin for treatment of DVT. Additionally, DOACs provide a practical benefit with ease of use (oral administration,) storage (no refrigeration/freezer), fewer medication interactions, and no requirement for laboratory monitoring (Long & Gottlieb, 2023).

Table 3. Efficacy and Safety Outcomes in Weighted Cohorts

Outcomes	Patients, No.	Events, No.	Person-years	Events per 100 person-years	Hazard ratio (95% CI)	*P* value
VTE recurrence						
LMWH	4607	398	1002.13	39.76	1.47 (1.14-1.90)	.003
Warfarin	4556	456	1526.48	29.89	1.46 (1.13-1.87)	.003
DOAC	4762	332	1609.44	20.62	1 [Reference]	NA
All-cause mortality						
LMWH	4607	225	1060.8	21.18	1.61 (1.15-2.25)	.005
Warfarin	4556	221	1627.76	13.59	1.19 (0.85-1.68)	.31
DOAC	4762	193	1696.33	11.36	1 [Reference]	NA
Hospitalization for major bleeding						
LMWH	4607	277	1035.84	26.73	2.27 (1.62-3.20)	<.001
Warfarin	4556	179	1609.61	11.1	1.12 (0.78-1.61)	.53
DOAC	4762	166	1681.52	9.88	1 [Reference]	NA
GI bleeding						
LMWH	4607	152	1041.21	14.64	1.72 (1.12-2.62)	.01
Warfarin	4556	119	1615.82	7.38	1.03 (0.67-1.59)	.89
DOAC	4762	121	1685.12	7.17	1 [Reference]	NA
Intracranial bleeding						
LMWH	4607	62	1058.49	5.88	2.72 (1.24-5.97)	.01
Warfarin	4556	31	1625.72	1.93	1.04 (0.45-2.45)	.92
DOAC	4762	31	1694.92	1.84	1 [Reference]	NA

Abbreviations: DOAC, direct oral anticoagulants; GI, gastrointestinal; LMWH: low-molecular-weight heparin; NA, not applicable; VTE, venous thromboembolism.

Efficacy and safety outcomes of various anticoagulants in weighted cohorts.
Source: Riaz et al., 2023

In the *Reduced-dosed Rivaroxaban in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism* trial patients completed 6 to 12 months of anticoagulation for VTE randomized to rivaroxaban or aspirin to prevent recurrence. Rivaroxaban patients experienced VTE recurrence of 1.5% (20mg), 1.2% (10mg) vs Aspirin patients experienced 4.45% recurrence (Weitz et al., 2017). Aspirin concerns also include increased risk of GI issues, bleed risks, and renal dysfunction concerns.

The Chest Journal guidelines (Stevens et al., 2021) support DOAC use:

- In patients offered extended-phase anticoagulation, we recommend reduced-dose DOAC over aspirin or *no* therapy and suggest rivaroxaban over aspirin.

- Patients with VTE (DVT leg or PE) we recommend apixaban, dabigatran, edoxaban, or rivaroxaban over vitamin K antagonist treatment-phase (first 3 months) anticoagulant therapy.
- In patients with VTE diagnosed in the absence of transient provocation (unprovoked VTE or provoked by persistent risk factor), we recommend offering extended-phase anticoagulation with a DOAC.

Adverse Effects of Apixaban

Per Agrawal et al., 2024 and Eliquis Patient Information, 2024, as an anticoagulant, apixaban's most common adverse effect is bleeding, with a 3% or less risk of major bleeding, and 2 to 4% risk of clinically relevant nonmajor bleeding.

Other less common adverse effects include nausea (3%), gingival hemorrhage (1% or less), hematuria (2% or less), hypermenorrhea (1%), anemia (3%), bruising/hematoma (1% to 2%), postprocedural hemorrhage (1% or less), rectal hemorrhage (1% or less), increased serum transaminases (1% or less), aspartate aminotransferase increased (1% or less), gamma-glutamyltransferase increased (1% or less), epistaxis (4% or less), and hemoptysis (1% or less). In rare instances (less than 1%), it can cause a hypersensitivity reaction.

Drug-drug Interactions with Apixaban

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, chronic NSAID, and selective serotonin reuptake or serotonin norepinephrine reuptake inhibitors, increases the risk of bleeding.

CYP3A4 and P-glycoprotein (P-gp) inhibitors increase apixaban exposure, (increasing bleed risk), and CYP3A4 and P-glycoprotein (P-gp) inducer medications decrease apixaban exposure and effectiveness.

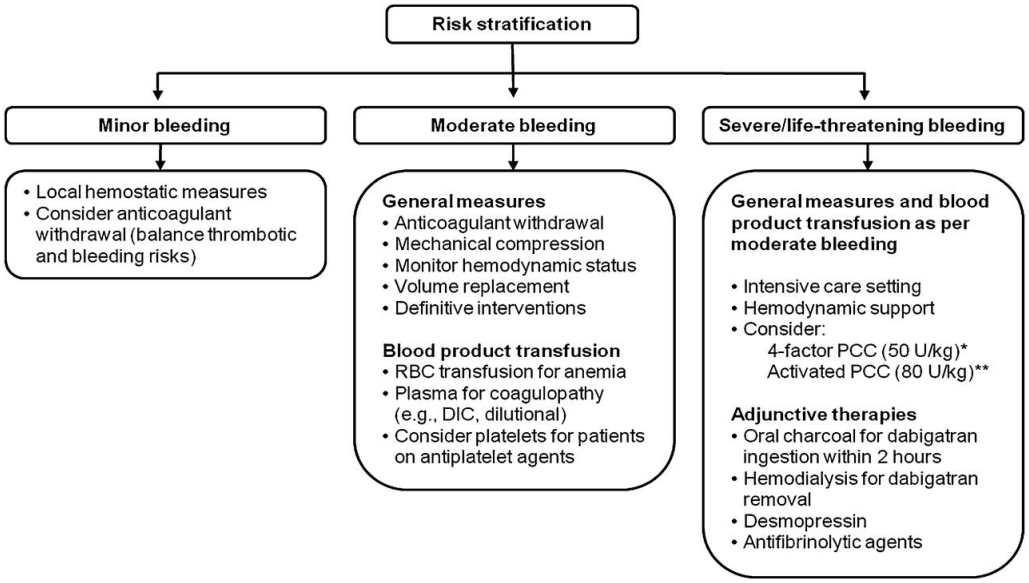
Thrombotic Events with Apixaban

Premature discontinuation of oral anticoagulant medicines, including apixaban, can increase the risk of thrombotic adverse events.

The biggest concern with all anticoagulant use is bleeding risk, and in spaceflight this concern is heightened during the challenges of launch, landing, and EVA as well as the concerns of limited capability to treat bleeding incidents. Currently the ISS carries 4 factor prothrombin complex concentrate (4F-PCC) and protamine as bleeding reversal agents. 4F-PCC can reverse bleeding associated with apixaban and no refrigeration is required. Coagulation factor Xa [recombinant] is a specific apixaban reversal agent available, however, it requires more complicated dose preparation (reconstitution from multiple vials) and dosing regimen of and follow-up infusion, as well as refrigeration storage. Coagulation factor Xa [recombinant] has shown better effectiveness and survival compared to 4F-PCC however the challenges it poses will need to be addressed

if included in the NASA med kit. Apixaban elimination half-life is approximately 12 hours and remains in the system 24-72 hours which some consider a short enough half-life that reversal agents are not necessary (Costa et al., 2022).

Bleeding Management



Suggested strategy for management of TSOAC-associated bleeding.
Source: Siegal et al., 2014

Summary, Risk Assessment and Proposed Spaceflight Venous Thrombosis Management

Based on expert opinion and the assessment of each of the risk factors for thrombosis, the following algorithm was developed to provide guidance for in-mission assessment and treatment of thrombus formation in weightlessness. The algorithm is based on early in-flight ultrasound testing to determine the flow characteristic of the left internal jugular.

Risk Factors

Family history (unprovoked thrombosis in immediate family members) and thrombophilia which increases thrombosis risk by 4-20X (Albagoush, 2023; Bezemer et al., 2009) are considered factors.

First- and second-generation estrogen-progestin combination oral contraceptive (COC) use which increases the thrombosis risk up to 3.2X (see table on p. 18) (Cockrum et al., 2022; LaVasseur et al., 2022; Pérez Gutthann et al., 1997) are considered factors.

Age was evaluated and based on the data that includes many comorbidities that astronauts do not have, it was not a factor in the algorithm. Incidence rates of VTE in patients aged ≥65 years are 3-fold higher than in patients aged 45–54 years (Akrivou et

al., 2022; Cushman et al., 2004) and may be a factor to consider for commercial space flyers who may have comorbidities.

Preflight Considerations

Preflight assessment should include consideration of the type of oral contraceptive use to minimize risk with DOACs if required in mission. The choice of a progesterone-only contraceptive (such as an IUD or the Nexplanon rod) may be preferred due to their lower risk for venous thrombosis over an estrogen-containing contraceptive to suppress/minimize menstrual bleeding on orbit. See table on page 19.

Crewmembers who have a history of unprovoked thrombosis in an immediate family member should consider not using oral estrogen therapy, and crewmembers positive for thrombophilia should not use hormone therapy or consider only using lower-risk hormone therapy.

In-flight Considerations

Based on expert opinion, stasis/stagnant flow was the most concerning as a pre-thrombotic indicator. Retrograde flow was not considered to be a main contributor to the formation of a thrombus but may be a concern if a thrombus does form.

Any observations such as Internal jugular swelling, facial edema beyond “nominal” spaceflight adaptation, and/or eyelid edema mydriasis, headache, and SANS symptoms should be considered as part of the risk assessment.

Medical Management

In-flight Ultrasound Assessment – Thrombosis Discovered

For those crew found to have thrombosis on orbit via ultrasound, treatment consists of administering an anticoagulant regardless of stasis status. Apixaban has been successfully used in past cases when a thrombus was detected in a crewmember and is carried in the in-flight medical kit, but alternates may be used. The recommended dosing is as follows:

- Treatment: Apixaban 10 mg twice a day for 7 days; afterwards 5 mg twice a day

Couturaud et al. (2024) provides evidence that reinforces the approach of transitioning to reduced doses of DOACs once the highest-risk period has passed.

Crewmembers using an estrogen-based COC should not discontinue its use if direct oral anticoagulants (DOACs) are administered to treat a suspected or confirmed thrombus due to the risk of abnormal uterine bleeding (AUB) (Baglin et al., 2012; Martinelli et al., 2016).

In-flight Operations Considerations for Crew with Thrombosis

- Decrease intensity of exercise prescription, do not use shoulder harness for T2

- Consider cancelling or delaying EVAs based on treatment outcomes and patient status

In-flight Ultrasound Assessment – No Thrombosis Discovered

Crew with no thrombosis but who have stasis with family history, thrombophilia, and/or who are taking any hormones that increase the risk of VTE (see Hormone Comparison Table on p. 18) should be provided prophylaxis:

- Prophylaxis dose: Apixaban 2.5 mg twice a day

Crew with no thrombosis but who have stasis and no family history and/or thrombophilia and who are not taking any hormones that increase the risk of VTE should be monitored more often, and hydration should be ensured.

Medical Kit Considerations

- Tranexamic acid should be added as part of an in-flight medical kit to be used in case of menorrhagia.
- Thrombolytics such as teneceteplase should be considered for inclusion to treat a pulmonary embolism if it were to occur.

Landing Considerations

Apixaban has a half-life of roughly 12 hours (with wide interpersonal variation) and if trauma (bleeding) does occur, the wound can be compressed, and the next dose(s) may be skipped until the trauma is under control. Reversal agents are difficult to administer in space, and if other anticoagulants are used, this should be considered.

It is recommended to stop apixaban at least 48 hours prior to landing in case of significant trauma during the landing event.

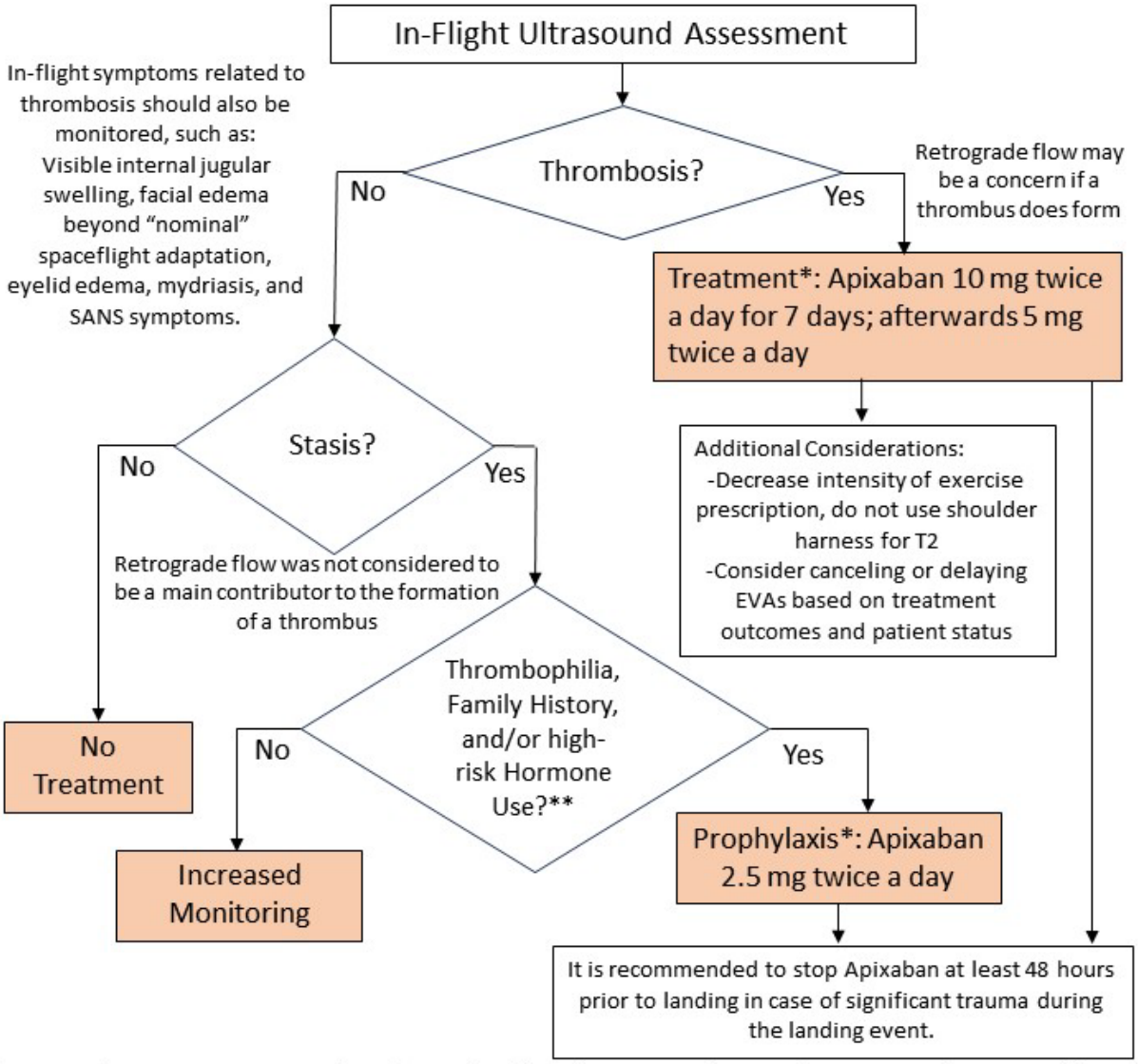
NOTE: These are guidelines, and each case presents differently, and treatment must be adjusted accordingly.

Refer to the diagram on the following page for treatment decision guidelines.

Proposed Spaceflight Veinous Thrombosis Management

Preflight Considerations

- Preflight assessment should include consideration of the type of oral contraceptive use to minimize risk with DOACs if required in mission. The choice of a progesterone-only contraceptive (such as an IUD or the Nexplanon rod) may be preferred due to their lower risk for veinous thrombosis over an estrogen-containing contraceptive to suppress/minimize menstrual bleeding on orbit.
- Crewmembers who have a history of unprovoked thrombosis in an immediate family member should consider not using oral estrogen therapy, and crewmembers positive for thrombophilia should not use hormone therapy or consider only using lower-risk hormone therapy.



*Crewmembers using an estrogen-based COC should not discontinue their use if DOACs are administered due to the risk of abnormal uterine bleeding (AUB) (Baglin et al., 2012; Martinelli et al., 2016).
**Unprovoked thrombosis in immediate family members; hormones that increase the risk of VTE (see Hormone Comparison Table on p. 18)

Areas for Further Consideration – Occupational Surveillance and Research

The working group recommended several areas for further investigation to assess feasibility and potential to mitigate the risk of thrombosis in spaceflight.

Improved Detection Capabilities

Preflight Factors Assessment

Assessment of preflight factors such as, but not limited to, terrestrial internal jugular flow stasis, internal jugular flow patterns during parabolic flight or tilt table data, and/or other biological aspects should be considered to identify individuals who may benefit from tailored countermeasures such as, but not limited to, being assessed earlier in flight and/or providing prophylactic treatment preflight.

Augmentation of Existing Venography Imaging

Augmentation of existing venography imaging should be reassessed to determine if any additional protocols should be conducted to better understand crew neck vascular and other anatomic structures and how they correlate to in-flight flow characteristics and thrombosis risk in the internal jugular veins during weightlessness.

In-flight Ultrasound Protocols

In-flight imaging protocols should be reassessed to determine if methods to determine flow volume can be achieved. It was noted that it is difficult to achieve and heavily dependent on operator skill but should be assessed (Elias et al., 2024). The valvular structure and function should be considered.

D-Dimer Screening

D-dimer screening is an immunoassay typically performed for rapid results in case of a suspected clot. D-dimer is generated during fibrinolysis and its presence is indicative of thrombin activity (Giannitsis et al., 2015). D-dimer can be present 2 hours after thrombus formation and has a half-life of 8 hours (Giannitsis et al., 2015). Despite D-dimer being a marker for fibrinolysis activity, it is not a marker for coagulation activity and a patient with positive screening for D-dimer should undergo further testing, specifically imaging (Pulivarthi & Gurram, 2014). The working group recommended the addition of D-dimer screening to pre-flight, in-flight, and post-flight medical exams and testing. The addition of a portable, handheld point-of-care D-dimer screening device on the ISS for in-flight testing was recommended, although feasibility of microfluidic/capillary action-based assay principles in microgravity would require further research.

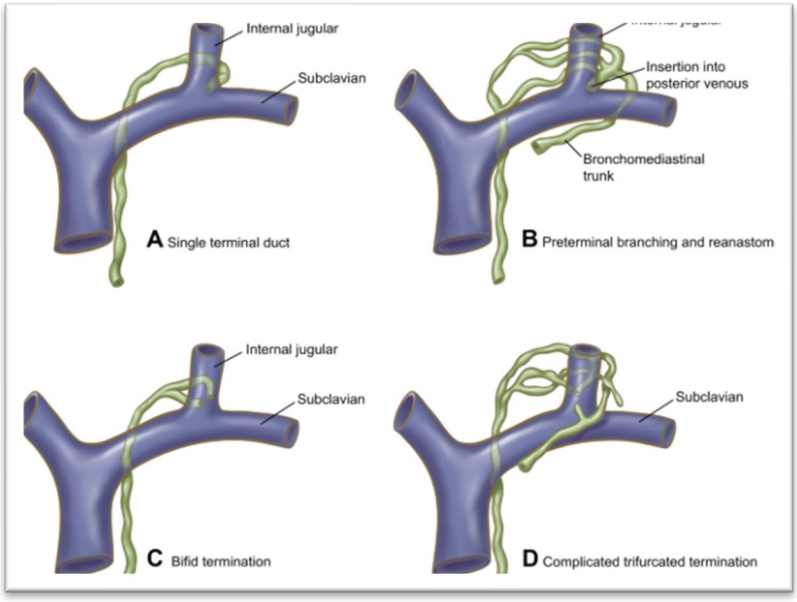
Quidel Roche LumiraDx

Portable, handheld D-Dimer screening devices
Source: Grover, 2024

Pathophysiology

Thoracic Duct Anatomy and Lymphatic Fluid Flow

Though the lymphatic flow is extremely low, the anatomy of the thoracic duct may influence the formation of thrombosis in the left jugular vein. The thoracic duct has variant anatomy in ~40% (range 30-50%) of the population (Liu, et al. 2006). The differences in the anatomy of the thoracic duct are depicted below. It is recommended to investigate the anatomy of the thoracic duct and determine whether it may be a factor in spaceflight thrombosis formation.



Differences in the anatomy of the thoracic duct.
Source: Shields et al., 2009

Countermeasures and Treatment

Countermeasures discussed were centered around modifying internal left jugular flow for crew that present with stasis.

Lower Body Blood Redistribution

Devices such as thigh cuffs, compression garments, or other mechanical methods should be investigated to determine whether they can be utilized long term to influence fluid shift in spaceflight and normalize the flow in the jugular veins for crew with stasis.

Müller Maneuver

The Müller maneuver consists of having the patient complete a forced inspiratory effort against an obstructed airway and has been shown to influence flow in the jugular vein in spaceflight. It was discussed whether a device could be used that can provide a method to partially obstruct the airway and cause forced inspiratory effort long term and/or modify the breathing process that causes favorable flow in the jugular for crew with stasis. The feasibly of a device was questioned but should be investigated.

External Compression of the Internal Left Jugular

It was discussed whether external compression of the muscle (such as the omohyoid muscle), the carotid sinus (carotid bulb) and/or other mechanisms such as the harness during exercise could contribute to the flow in the jugular. Preliminary testing in space did not show an impact of the exercise harness; however, additional investigation should be conducted to help refine the recommendation of not using the harness is a thrombosis is found in mission.

Lower-dose Anticoagulation

At the 2024 American Society of Hematology (ASH) Annual Meeting & Exposition, Couturaud et al. presented the first robust evidence demonstrating that low-dose DOAC is as effective as full-dose DOAC for preventing recurrent thrombosis and is associated with a lower risk of bleeding. This should be investigated further, as it is relevant to the algorithm for long-term VTE treatment in crewmembers on long-duration missions.

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