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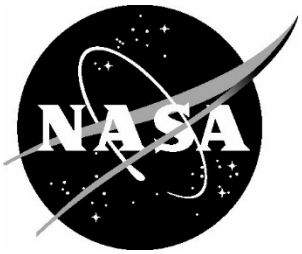

NASA Risk of Venous Thromboembolism in Spaceflight
Outcomes of Working Group Meeting – April 2026

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June 2026

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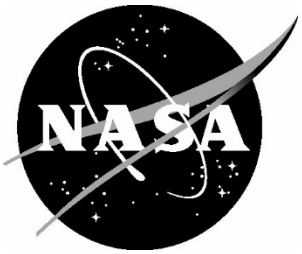

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Contents

Executive Summary

Following the diagnosis of venous thromboembolisms (VTEs) of astronauts during in-flight missions on the International Space Station, and the additional data gathered revealing altered blood flow status within a cohort of astronauts, NASA's Office of the Chief Health and Medical Officer initiated a working group of internal and external experts to review case data and discuss updates to the Clinical Practice Guidelines for preventing and treating VTE in spaceflight, as well as identify potential mechanisms contributing to the observed phenomenon and pathways forward to inform future monitoring and treatment for VTEs in-flight.

The following is a summary of the working group's recommendations:

- The working group's conclusions emphasized that stasis in the left internal jugular vein (IJV) is consistently viewed as a dominant risk factor for VTE in microgravity, though there is active debate regarding the relative contributions of slow qualitative flow, endothelial factors and/or retrograde flow.
- Limitations of current in-flight ultrasound capabilities to accurately measure stasis/slow flow was cited as a concern, especially if using only stasis as a factor for indicating the need for prophylaxis.
- Additional review of assessing stasis with ultrasound in-flight was recommended.
- After reviewing the risk factors, additional discussions following the working group led to the majority of the panel agreeing that stasis and retrograde flow warranted use of prophylaxis.
- The working group also recommended assessing all other risk factors other than stasis to also determine when prophylaxis is warranted.
- Based on a literature review and summary of the panel contributions, the following *VTE Risk Score for Astronauts Algorithm* was developed, which includes providing anticoagulation prophylaxis for stasis alone, or a combination of other thrombosis risk factors that are weighted by terrestrial literature.

VTE Risk Score for Astronauts Algorithm

Risk Factor	Scoring	Increased Risk
Pre-flight Assessments		
Age of astronaut (Raskob et al., 2014; NIH, 2022)		
Over 40 years of age	+1 point	Increases ~55% from ages 40-49 to 50-59 years
Over 50 years of age	+2 points	Increases ~160% from ages 50-59 to 60-69 years
Family History (Bezemer et al., 2009)		
First-degree relative < 50 years of age with an unprovoked VTE	+1 points	Up to 2-fold increase
Two+ first-degree relatives (at least one <50 years of age) with an unprovoked VTE	+2 points	Up to 4-fold increase
Thrombophilia (Albagoush, 2023)		
Factor V Leiden heterozygous	+2 points	4.9-fold (3-8-fold) increase
Factor V Leiden homozygous	+8 points	16-fold increase
Factor V Leiden with other thrombophilia conditions	+10 points	20-fold increase
Protein C deficiency	+3 point	7-fold increase
Protein S deficiency	+3 point	7-fold increase
Antithrombin III deficiency	+10 points	16-fold (up to 20-fold) increase
Prothrombin gene mutation, heterozygous	+2 point	3.8-fold increase
Blood Type (Engbers, Van Hylckama Vlieg, & Rosendaal, 2010)		
Non-O allele of the ABO genotype	+1 point	2-fold increase
Higher-risk Hormone Use (See Hormone Comparison Table)		
Use of 'low/no increased risk' hormone	+1 point	Minimal
Use of 'some increased risk' hormone	+2 points	2 to 3.2-fold increase
Use of 'moderate increased risk' hormone	+2 points	3.8-fold increase
In-flight Assessments		
Stasis (less than 10 cm/s blood flow velocity) or retrograde flow (CDC, 2026; Kuipers et al., 2007; Wang et al., 2020; Halsema & Mcmahon, 2023; Marshall-Goebel et al., 2019)	+4 points	2 to 4-fold increase (evidence from long-haul flights) 4 to 7-fold increase (evidence from jugular venous stasis associated with cancer) See section below titled *Stasis and Retrograde Flow*
D-dimer Values	+2 points	≥60% increase from established in-flight D-dimer baseline level. See section below titled *D-dimer Values*

1 point = no additional action
2-3 points = increased monitoring
4-6 points = prophylactic apixaban
> 6 points = need clinical assessment

Abbreviated Summary Report

Supporting Evidence for VTE Risk Score for Astronauts Algorithm

The following sections of the Executive Summary present the abbreviated evidence report for each risk factor included in the Risk Score for Astronauts guideline and relevant clinical practices for prophylaxis and treatment with Apixaban. The remaining sections of the document include further detailed evidence reports as well as additional areas of consideration to inform treatment and enhance occupational surveillance for Spaceflight Venous Thrombosis.

VTE Risk Factors

Age – A large systematic literature review of global VTE burden found that the risk of VTE increased by approximately 55% from ages 40-49 to 50-59 years, and approximately 160% increase from ages 50-59 to 60-69 years (Raskob et al., 2014). There is some evidence to suggest that there is a notable increase in risk of VTE beyond 40 years of age, with the National Heart, Lung, and Blood Institute stating that the chance of developing a VTE nearly doubles every 10 years after age 40 (NIH, 2022).

Family History – A history of unprovoked venous thrombosis in first-degree family members has found to increase the risk of developing VTE, particularly if the family member was < 50 years of age at time of diagnosis, with a 2-fold increase in risk. Multiple first-degree relatives with a history of VTE, with at least one < 50 years of age, leads to a 4-fold increase in risk (Bezemer et al., 2009).

Thrombophilia – Thrombophilias, either acquired or hereditary, can be identified in approximately 10% of the general population and is seen in a number of patients presenting with VTE. These conditions can increase the risk of developing VTE by anywhere from a 3.9 – 20-fold.

Blood Type – Non-O alleles of the ABO genotype have been observed to increase risk of VTE by approximately 2-fold compared with O alleles in the general population. This is partially explained by the fact that Factor VIII and von Willebrand factor concentrations are higher in non-O than O-group blood types (Engbers, Van Hylckama Vlieg, & Rosendaal, 2010).

Higher-risk Hormone Use – Hormone management or suppression is commonly used by astronauts and certain hormones increase the risk of developing VTE. The Hormone Comparison Table on page 11 of this document details various types of hormone usage, ranging from a 2-fold to 3.8-fold increase in risk.

Stasis and Retrograde Flow – Altered blood flow in astronauts has been observed in both the left and right internal jugular veins concomitant with vessel distension. While the

clinical risk associated with altered blood flow and developing VTE remains unquantifiable both terrestrially and in spaceflight, abnormal blood flow is conjectured to be a potential mechanism associated with developing VTE. Virchow's triad proposes VTE occurs as the result of: Alterations in blood flow (i.e., stasis), vascular endothelial injury/changes, and/or alterations in the constituents of the blood leading to hypercoagulability (i.e., hereditary predisposition or acquired hypercoagulability). Reduced blood flow and stasis allow the accumulation of procoagulant proteases, such as thrombin, that may overcome the local anticoagulant pathways and induce thrombosis (Mackman, 2012). Evidence from long-haul travel (4+ hours) suggests a 2-to-4-fold increase in risk (CDC, 2026; Kuipers et al., 2007) and jugular venous stasis associated with cancer has a 4-to-7-fold increased risk of developing VTE (Wang et al., 2020; Halsema & Mcmahon, 2023). It remains unclear the contribution of altered blood flow and hemodynamics observed in spaceflight to the risk of VTE in-flight. Discussions by the working group panel identified difficulties in obtaining consistent blood flow measurements utilizing current ultrasound methodology. The hypothesis is that cases of left IJV stasis share inherent anatomical features that can be used as predictor variables.

D-dimer Values – D-dimer levels can be detected in a simple blood test and can give surveillance information when a blood clot is suspected (Clevland Clinic, 2021). NASA does not routinely test D-dimer levels in astronauts. There are no existing adequate in-flight testing methods, and it is considered an imprecise test not singularly adequate for clot diagnosis, but this practice may change. In-flight D-dimer could be helpful as a surveillance tool, allowing attention to be brought to a clot situation earlier and when used in conjunction with other information including imaging (in-flight US), symptoms, and known risk factors, can assist with clot diagnosis and monitoring. Future implementation must establish a baseline D-dimer level as early as possible in-flight (once fluid shifts settle) at approximately L+ 14 days and begin surveillance testing at L+30, with the need to consider additional test schedules to continue surveillance. Levels observed ≥60% increase from baseline level would lead to potential prophylactic Apixaban use, in combination with other risk factors (Hansen et al., 2021).

Apixaban for Prophylaxis and Treatment in Spaceflight

NASA held a VTE working group in 2024 that recommended Apixaban as safe and effective treatment for detected in-flight clots (VTE Summary Report, 2025). Further evaluation has determined that Apixaban is beneficial when used at a lower dose to prevent clot formation in individuals with higher risk physiology or risk factors. The usual recommended treatment dose is 5 mg orally twice daily, in patients with at least 2 of the following characteristics: age >80 years, body weight <60 kg, or serum creatinine >1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily.

NASA's recommended prophylactic dose for high-risk astronauts is 2.5 mg twice daily, with dosing starting on the 3rd day of flight or once the astronaut has acclimated to the microgravity environment as determined by the flight surgeon. ***The overall risk of major bleeding related to Apixaban use is approximately 1.4%/year*** (Connolly et al., 2011)**.** Preventive dose references:

- AMPLIFY-EXT Apixaban 2.5mg vs. 5mg – Outcome recurrent VTE/death 3.8% vs. 4.2%; Major Bleeding 0.2% vs. 0.1%; Clinically-Relevant Non-Major Bleeding (CRNMB) 3% vs. 4.3% (Agnelli et al., 2013)
- DeRemer analysis 2.5mg vs. 5mg Apixaban – Outcome recurrent VTE 0.3% vs. 0.47%; Major bleeding events 1.49% vs. 2.23% (DeRemer et al., 2022)
- American College of Chest Physicians (CHEST) guidelines on Apixaban for VTE therapy recommend that extended phase therapy for unprovoked VTE prevention provide direct oral anticoagulant (DOAC) in reduced doses e.g., Apixaban 2.5mg twice daily over full dose (American Family Physician, 2022).

Several studies show the efficacy of Apixaban in VTE prevention while maintaining a low bleeding risk.

Study	Outcome	Major Bleeding or CRNMB
AVVEROES Trial Apixaban 5mg vs. aspirin 81-324mg (Connolly et al., 2011)	Stroke or systemic embolism 1.6% vs. 3.7%	Major Bleeding 1.4% vs. 1.2% CRNMB 3.1% vs. 2.7%
AMPLIFY-EXT Apixaban 2.5 vs. 5mg (Arifi et al., 2026)	Symptomatic VTE 1.7% vs. 1.7%	Major bleeding 0.2% vs. 0.1% CRNMB 3% vs. 4.2%
HI-PRO Trial Apixaban 2.5 mg vs. placebo (Pfeferman et al., 2026)	First symptomatic recurrent VTE 1.3% vs. 10%	Major bleeding 0.3% vs. 0% CRNMB 4.8% vs. 1.7%
ARISTOTLE Apixaban 5mg vs. Warfarin (Granger et al., 2011)	Ischemic, hemorrhagic stroke or systemic embolism 1.27% vs. 1.6%	Major Bleeding 2.13% vs. 3.09%

Recent studies have shown that DOAC medications like Apixaban have fast onset and clearance and can be safely interrupted if they are managed correctly. Berkowitz and Moll (2017) describe personalized pharmacokinetic/pharmacodynamic (PK/PD) studies which aids patient-specific management by determining individuals' drug elimination half-life and plasma drug concentration levels to minimize bleeding risk. Thus, astronauts will discontinue prophylactic Apixaban 24 hours prior to conducting high-risk extravehicular activities (EVAs) or based on individual Apixaban PK/PD study administration plan and will restart medication upon EVA completion. Additionally, astronauts will discontinue Apixaban use 48 hours prior to landing due to risks associated with landing.

Apixaban Versus Aspirin for VTE Prevention

Apixaban provides substantially better VTE recurrence prevention than aspirin while carrying comparable bleeding risk. The AVERROES trial of 5,500 atrial fibrillation patients, unsuitable to take Warfarin, compared Apixaban vs. aspirin to determine efficacy with stroke or systemic embolism occurrence. The trial concluded early based on treatment benefit in favor of Apixaban (Connolly et al., 2011). The EINSTEIN CHOICE trial also supported the superiority of DOAC (rivaroxaban) versus aspirin in preventing VTE reoccurrence without significant increase in bleeding rates (Weitz et al., 2017).

Table 3. Rates of Study Outcomes in the Two Treatment Groups.*

Outcome	Apixaban (N=2808)		Aspirin (N=2791)		Hazard Ratio with Apixaban (95% CI)	P Value
	no. of patients with first event	*%/yr*	*no. of patients with first event*	*%/yr*		
Stroke or systemic embolism	51	1.6	113	3.7	0.45 (0.32–0.62)	<0.001
Stroke, systemic embolism, or death	143	4.6	223	7.2	0.64 (0.51–0.78)	<0.001
Stroke, systemic embolism, myocardial infarction or death from vascular cause	132	4.2	197	6.4	0.66 (0.53–0.83)	<0.001
Stroke, systemic embolism, myocardial infarction, death from vascular cause, or major bleeding event	163	5.3	220	7.2	0.74 (0.60–0.90)	0.003
Stroke†	49	1.6	105	3.4	0.46 (0.33–0.65)	<0.001
Ischemic	35	1.1	93	3.0	0.37 (0.25–0.55)	<0.001
Hemorrhagic	6	0.2	9	0.3	0.67 (0.24–1.88)	0.45
Unspecified	9	0.3	4	0.1	2.24 (0.69–7.27)	0.18
Disabling or fatal	31	1.0	72	2.3	0.43 (0.28–0.65)	<0.001
Systemic embolism	2	0.1	13	0.4	0.15 (0.03–0.68)	0.01
Myocardial infarction	24	0.8	28	0.9	0.86 (0.50–1.48)	0.59
Death						
From any cause	111	3.5	140	4.4	0.79 (0.62–1.02)	0.07
From vascular cause	84	2.7	96	3.1	0.87 (0.65–1.17)	0.37
Hospitalization for cardiovascular cause	367	12.6	455	15.9	0.79 (0.69–0.91)	<0.001
Bleeding event						
Major	44	1.4	39	1.2	1.13 (0.74–1.75)	0.57
Intracranial	11	0.4	13	0.4	0.85 (0.38–1.90)	0.69
Subdural‡	4	0.1	2	0.1	—	—
Other intracranial, excluding hemorrhagic stroke and subdural‡	1	<0.1	2	0.1	—	—
Extracranial or unclassified	33	1.1	27	0.9	1.23 (0.74–2.05)	0.42
Gastrointestinal	12	0.4	14	0.4	0.86 (0.40–1.86)	0.71
Non-gastrointestinal	20	0.6	13	0.4	1.55 (0.77–3.12)	0.22
Fatal§	4	0.1	6	0.2	0.67 (0.19–2.37)	0.53
Clinically relevant nonmajor	96	3.1	84	2.7	1.15 (0.86–1.54)	0.35
Minor	188	6.3	153	5.0	1.24 (1.00–1.53)	0.05

* The percent per year is the rate per 100 patient-years of follow-up. All analyses were based on the time to a first event; patients could have more than one event.
† Stroke included ischemic and hemorrhagic (i.e., primary intracerebral bleeding) types; some strokes could not be classified (unspecified). Hemorrhagic stroke is also included in the categories of major bleeding and intracranial bleeding. Disabling or fatal stroke was defined by a modified Rankin score of 3 to 6. The modified Rankin score is a measure of the severity of stroke on a scale from 0 (no symptoms or disability) to 6 (death).
‡ Hazard ratios and P values were not calculated for these events because there were so few events.
§ Bleeding events were reported as fatal by the investigator and were confirmed at adjudication.

Source: Connolly et al., 2011

Full Summary Report

Working Group Attendees

NASA Presenters

Dr. Tyson Brunstetter – SANS Clinical Lead – *Eyes/Vision, Space and Occupational Medicine Branch*

Dr. Joseph Dervay – Flight Surgeon, *Space Medicine Operations Division*

Dave Francisco – Technical Fellow for Human Spaceflight Standards, *Office of the Chief Health & Medical Officer*

Dr. Michael Greene – Flight Surgeon, *Space Medicine Operations Division & Operational Space Medicine, Canadian Space Agency (CSA)*

Dr. Craig Kutz – Flight Surgeon, *Space Medicine Operations Division*

Dr. Jason Lytle – Integrated Physiologist, *Biomedical Research & Environmental Sciences Division*

Dr. Derek Nusbaum – Flight Surgeon, *Space Medicine Operations Division*

Dr. James Pavela – Physician, *Space & Occupational Medicine Branch*

Dr. J.D. Polk – Chief Health & Medical Officer, *Headquarters*

Dr. Ashot Sargsyan – Physician, *Mission Operations Branch*

Invited Reviewers

Dr. Sergi Vaquer Araujo – Lead Space Medicine Team & HRE Chief Medical Officer, *European Space Agency*

Dr. Hayley Arron – Post-doctoral Research Fellow, *European Space Agency*

Dr. Serena Auñón-Chancellor – Clinical Professor, *Texas A&M Health*

Dr. Jeffrey S. Berger – Director of the Center for the Prevention of Cardiovascular Disease, *NYU Langone Health*

Dr. Eric Bershad – Professor of Neurology, Neurosurgery and Space Medicine Section of Vascular Neurology and Neurocritical Care; Director of Commercial Astronaut Data Repository, *Baylor College of Medicine*

Dr. David Charnock – Assistant Professor of Surgery, *Dartmouth Geisel School of Medicine*

Dr. Mark Crowther – Chair and Distinguished University Professor, *McMaster University Department of Medicine*

Dr. Jon-Emile S. Kenny – Co-founder and Chief Medical Officer, *Flosonics Medical*

Dr. Larry Kramer – Professor, *McGovern Medical School UTHealth Houston*

Dr. Raffi Kuyumjian – Flight Surgeon & Chief Medical Officer, *Canadian Space Agency (CSA)*

Dr. Stephan Moll – Professor of Medicine, Division of Hematology-Oncology, *University of North Carolina School of Medicine*

Dr. Steven Nissen – Chief Academic Officer of the Heart, Vascular, and Thoracic Institute, *Cleveland Clinic*

Dr. Mark Joshua Rosenberg – Assistant Professor, Department of Neurology; Director, Division of Aerospace and Performance Neurology; Campus Director, South Carolina Space Grant Consortium, *Medical University of South Carolina*

Dr. Terje Sæhle – Chief Medical Officer, *Norwegian Civil Aviation Authority & Medical Board Member, European Space Agency*

Dr. Adnan Siddiqui – Distinguished Professor and Vice Chairman in the Department of Neurosurgery, *State University of New York at Buffalo's Jacobs School of Medicine and Biomedical Sciences*

Dr. Gavin Travers – Post-doctoral Research Fellow, *European Space Agency*

Dr. Philip Wells – Professor, Chair and Chief, Department of Medicine, *The University of Ottawa*

Dr. Mario Zamora – *Exentris PLLC, SANS & Ocular Subworking Group*

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Michael Barratt
Judith-Irina Buchheim
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Steven Grover
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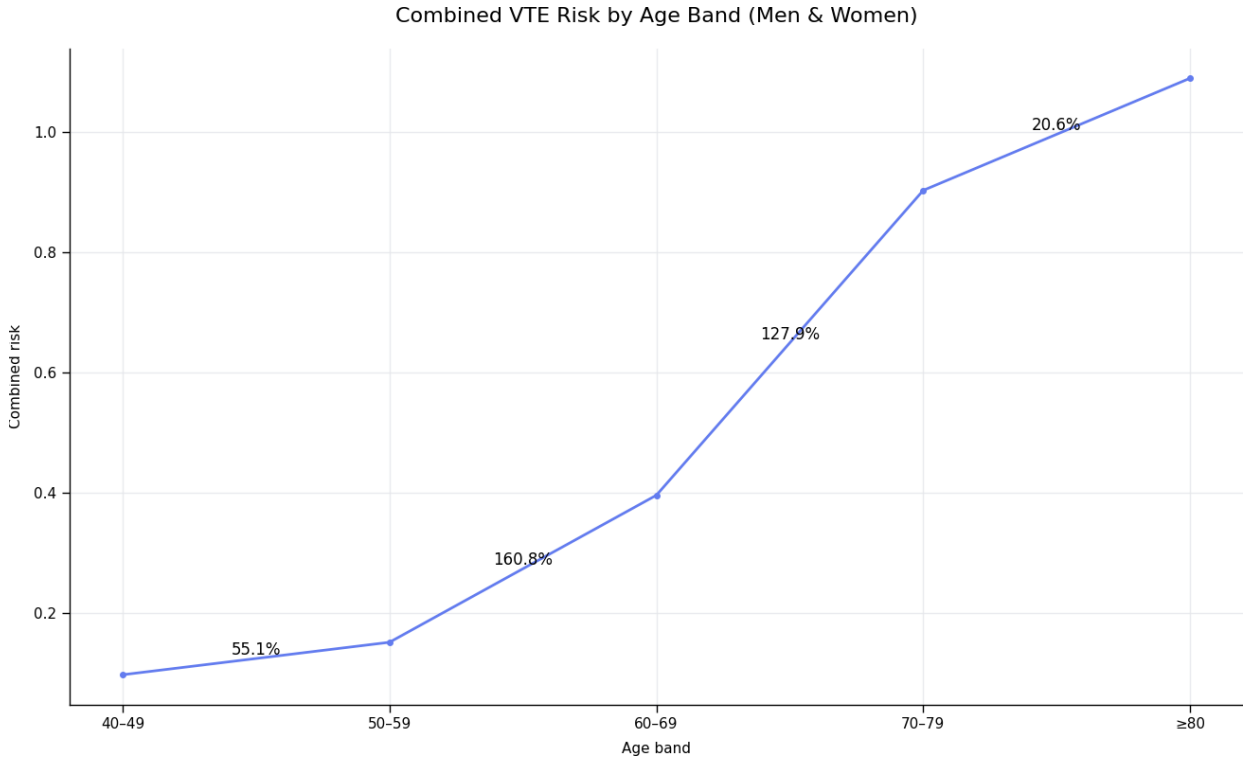
Sara Mason
Kathleen McMonigal
Vincent Michaud
Shannan Moynihan
Charolette Pearce
Terrence Taddeo
Sarah Taoufik

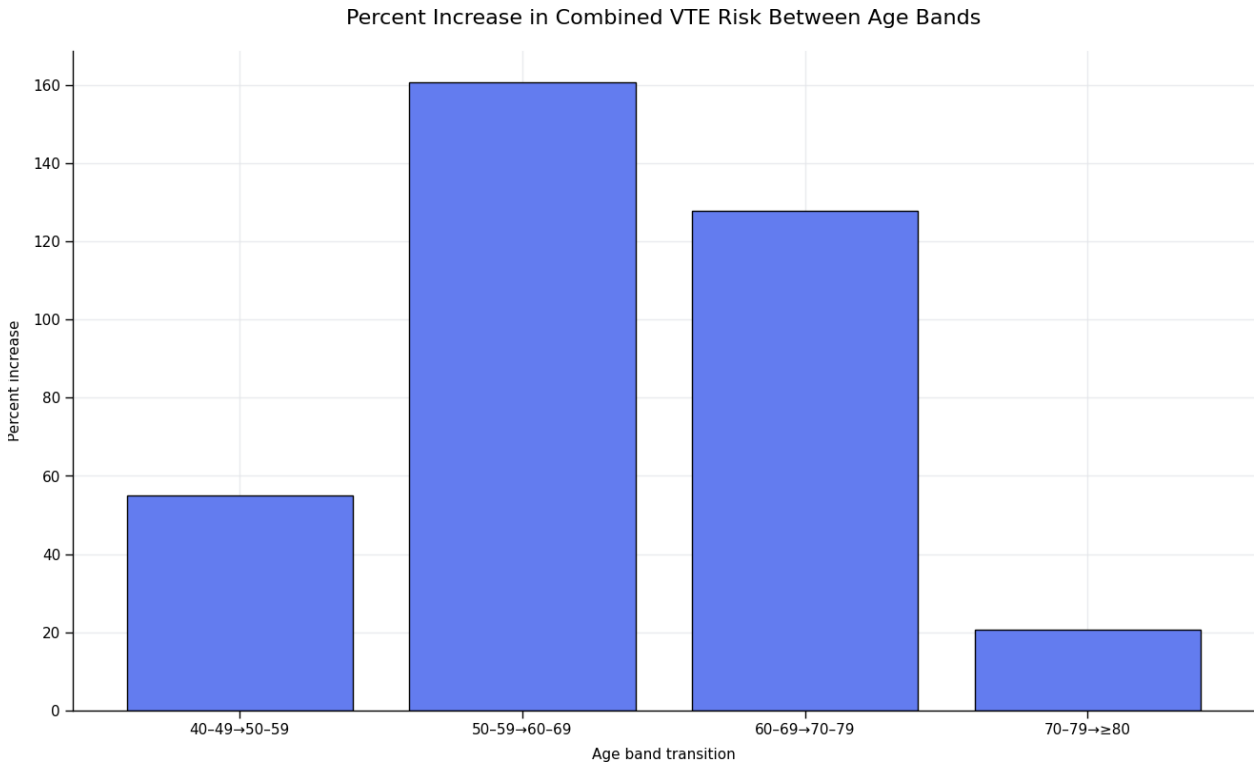
Evidence for VTE Risk Factors

Age

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). A large systematic literature review of global VTE burden found that the risk of VTE increased by approximately 55% from ages 40-49 to 50-59 years, and approximately 160% increase from ages 50-59 to 60-69 years. Women's risk increases more sharply than men from ages 50-59 to 70-79 (Raskob et al., 2014). A report by Silverstein et al. (2007) found that incidence rates increase dramatically at about age 55 and are 1000-fold higher from 45 to 80 years of age. The European Society of Human Reproduction and Embryology (ESHRE) Workshop Group observe a strong age gradient in VTE risk, with the risk doubling from age 25 to age 50 (Eichinger et al., 2013). The MAISTHRO registry reports that unprovoked VTE occurred less frequently among patients under the age of 40, and over the age of 40, the proportion of unprovoked VTE remained constant (Linnemann et al., 2014).

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). While many of the common comorbidities observed in older populations do not apply to the astronaut population, there is some evidence to suggest that there is a notable increase in risk of VTE beyond 40 years of age, with the National Heart, Lung, and Blood Institute stating that the chance of developing a VTE nearly doubles every 10 years after age 40 (NIH, 2022), and thus should be considered when determining potential prophylactic treatment for astronauts when combined with other risk factors.





Graphs adapted from: Raskob et al., 2014

First-degree Family History

A history of unprovoked venous thrombosis in first-degree (i.e., siblings, parents, or children) family members is considered a risk factor for VTE. The 2025 VTE Summary Report describes the increase in risk of VTE in relation to family history as:

- First degree relative with history of VTE < age 50 – Up to 2-fold increase in risk
- Multiple first-degree relatives with history of VTE – Up to 4-fold increase in risk
- 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 increase in risk

Source: Bezemer et al., 2009

Further investigation into the first-degree family history of unprovoked VTE established an association between younger age of diagnosis and a family history of VTE, with one summary by Couturaud et al. (2014) establishing that patients with a first occurrence of unprovoked VTE at < 45 years of age were strongly correlated with a family history of VTE compared to older VTE patients. Zoller et al. (2011) surmises that there is a diminishing impact of family history as a risk factor for VTE as one ages.

Thrombophilia

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 is seen in a number of patients presenting with VTE. The current 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

Source: Albagoush, 2023

Blood Type

Non-O alleles of the ABO genotype have been observed to increase risk of VTE by approximately 2-fold compared with O alleles in the general population. This is partially explained by the fact that Factor VIII and von Willebrand factor concentrations are higher in non-O than O-group blood types (Engbers, Van Hylckama Vlieg, & Rosendaal, 2010).

Higher-risk Hormone Use

Use of certain hormones, such as combined oral contraceptive pills, is considered a risk factor for VTE. Hormone management or suppression is commonly used by astronauts, as the logistics of menstruating during spaceflight can be challenging (waste disposal, volume/mass hygiene products). Since the first reported VTE case, NASA flight surgeons have been prescribing "lower risk" hormone therapy. The 2025 VTE Summary Report describes in detail the relationship between various hormone usage and the increased risk of VTE.

Hormone Comparison Table

Hormone Preparations	Progesterone	Estrogen (mcg)	VTE Risk
Progestin only pills	Norethindrone	None	Low/No increased risk[1]
LNG IUD	Levonorgestrel	None	Low/No increased risk[2]
Implant	Etonogestrel	None	Low/No increased risk[3]
Hormone Testosterone micronized 2mg	None	None	Low/No increased risk
Testosterone Cypionate injections	None	None	Low/No increased risk
Hormone Therapy Estrogen		Estradiol patch	Low/No increased risk[1]
		Premarin oral	2-fold increase[1]
Progesterone	Micronized progesterone 100mg (Oral)	None	Low/No increased risk[5]
	Medroxyprogesterone depot 150mg	None	2.6-fold increase[2]
2nd Generation Progesterone CoC	Levonorgestrel	Ethinyl estradiol (20,10)	2.8-fold increase[4]
		Ethinyl estradiol (20)	
		Ethinyl estradiol (30)	
		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)	
		Ethinyl estradiol (30)	
		Ethinyl estradiol (20,30,35)	
	Norethisterone	-	
	Norethindrone	Ethinyl estradiol (35)	
	Ethynodiol diacetate	Ethinyl estradiol (35)	
		Ethinyl estradiol (50)	
	Norgestrel	Ethinyl estradiol (30)	
		Ethinyl estradiol (50)	
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			

Stasis and Retrograde Flow

Altered blood flow in astronauts 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. 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 with four possible grades ranging from forward flow to retrograde flow (Marshall-Goebel et al., 2024).

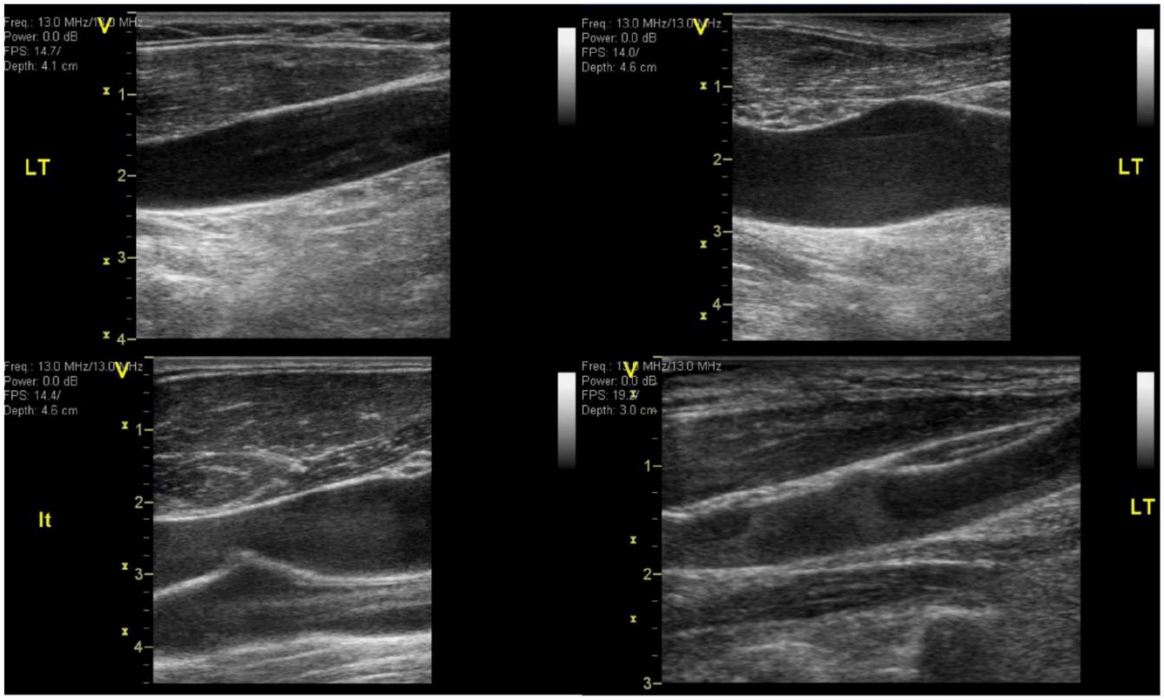
Terrestrial science and research have postulated some mechanisms that may be associated with reduced blood flow and stasis, and risk of developing VTE. Reduced blood flow and stasis allow the accumulation of procoagulant proteases, such as thrombin, that may overcome the local anticoagulant pathways and induce thrombosis (Mackman, 2012). This may explain the increased rate of VTE associated with surgery, hospitalization, paralysis, long-haul travel, cancer, obesity, age, and pregnancy.

Thrombus formation and propagation depend on the presence of abnormalities of blood flow, blood vessel wall, and blood clotting components, known collectively as Virchow's triad. Virchow's triad proposes VTEs occur as the result of: Alterations in blood flow (i.e., stasis), vascular endothelial injury/changes, and/or alterations in the constituents of the blood leading to hypercoagulability (i.e., hereditary predisposition or acquired hypercoagulability). Abnormalities of blood flow or venous stasis normally occur after prolonged immobility or confinement to bed. Venous obstruction can arise from external compression by enlarged lymph nodes, bulky tumors, or intravascular compression by previous thromboses (Turpie, Chin, & Lip, 2002).

Evidence from long-haul travel (4+ hours) suggests a 2-to-4-fold increase in risk (CDC, 2026; Kuipers et al., 2007) and jugular venous stasis associated with cancer has a 4-to-7-fold increased risk of developing VTE (Wang et al., 2020; Halsema & Mcmahon, 2023).

A study conducted with 31 long-duration mission NASA astronauts examined for blood flow abnormalities and compared ultrasound scans of the right and left internal jugular veins (IJV) pre-flight, L+30 days, L+60 days, and R-6 weeks. Statistically significant increases in right and left cross sectional area of the IJV and significant decreases in peak velocity in both right and left IJV were observed, with the right IJV appearing to take on some of the outflow from the left IJV. A dramatic drop in peak velocity was observed in the left compared to the right IJV.

The observed Left Atrial Spontaneous Echo Contract (LA-SEC) is associated with increased concentrations of hematocrit, fibrinogen, and slow blood flow (Prasad et al., 2023), and is thought to be the visualization of red blood cell aggregation (Tanaka & Saijo, 2007). LA-SEC scoring has the highest Receiver Operating Characteristic - Area Under the Curve (ROC AUC) for stroke in those with atrial fibrillation and is an independent predictor of thromboembolic risk in patients with atrial fibrillation and associated with an increase in embolism from 3-12% per year (Zhao et al., 2016).



Spontaneous echo contrast (SEC) grades 1–4. Longitudinal sonographic images of the left internal jugular vein with differing flow patterns recorded during in-flight exams. **Top left:** 1 – anechoic; **top right:** 2 – mild echogenicity; **bottom left:** 3 – mild-to-moderate diffuse echogenicity; **bottom right:** 4 – moderate echogenicity with organized pattern. Source: Pavela et al., (2022)

Pre-flight terrestrial scans of the 31 astronauts revealed mainly grades of 1 and 2. In-flight scans revealed grades of 3 and 4 predominantly in the left IJV, with these scores generally persisting throughout the subsequent in-flight scans. A case is defined as abnormal when mean peak velocity is less than 10 cm/s anterograde. In summary, 8 of the 31 subjects were identified as having left IJV flow anomaly, with 6/8 with at least one episode of retrograde flow, 5/8 consistently retrograde or zero, and 1/8 creeping (+) or (-), mean (+), and 2/8 never showing retrograde. In the subjects with extremely slow flow, 8 had left IJV valves despite SEC slow flow and 2/8 had no identifiable valves in the right IJV.

Astronaut #	Case status	Left IJV SEC				Right IJV SEC			
		TB	Ex 1	Ex 2	Ex 3	TB	Ex 1	Ex 2	Ex 3
1		1	2	2	1	1	1	1	1
2	✓	1	4	4	4	1	2	1	1
3	✓	1	3	3	3	1	1	1	1
4	✓	1	3	4	---	1	1	2	---
5		1	1	3	1	1	1	2	1
6		1	1	1	1	1	1	1	1
7	✓	3	4	4	4	2	2	1	1
8		1	1	1	2	1	1	1	2
9	✓	1	4	4	4	1	1	1	2
10		2	1	2	2	1	1	1	1
11	✓	1	4	4	4	1	1	1	1
12		1	1	1	1	1	1	1	1
13		2	4	4	4	2	1	1	2
14	✓	2	4	4	4	2	1	1	2
15		1	2	2	2	1	2	2	1
16	✓	2	4	3	---	1	2	1	---
17		1	2	---	---	1	2	---	---
18		2	2	---	---	1	1	---	---
19		1	2	2	2	1	2	1	1
20		1	1	3	1	1	1	2	1
21		1	2	3	2	1	1	1	1
22		1	2	3	2	1	1	1	1
23		1	2	2	3	1	2	2	2
24		2	2	2	3	1	1	2	2
25		3	2	1	1	1	1	1	1
26		1	2	2	---	1	1	1	---
27		1	2	1	---	1	2	1	---
28		2	3	2	3	1	1	1	1
29		2	3	2	3	1	1	1	1
30		1	1	1	1	1	1	1	1
31		2	2	1	1	1	2	2	1

It remains unclear the contribution of altered blood flow and hemodynamics observed in spaceflight to the risk of VTE in-flight. Discussions by the working group panel identified difficulties in obtaining consistent blood flow measurements utilizing current ultrasound methodology.

Left IJV Peak Flow Velocities Mapped to Anatomical Asymmetry Assessment

NASA performed an assessment of 31 previously flown individuals' data from in-flight pulse doppler waveform peak velocities and pre-flight head MRI combined with MR venography (MRV). A statistical examination of all pre-flight, in-flight, and post-flight scans were utilized to create a predictive model on who may develop stasis and or retrograde flow in-flight based on the ratio of IJV diameters at the skull base. The analysis indicated that when right to left ratio of IJV diameters at the skull base were <1.55 cm (of 15 individuals), no stasis or retrograde flow was observed with peak flow between 18-46 cm/s. When the ratio was >1.55 cm, 50% (8/16 individuals) experienced stasis (<10 cm/s) and/or retrograde flow. The remainder (8/16 individuals) experienced peak flow velocities of 18-70 cm/s.

The observed in-flight cases of VTE, whom were not part of the cohort of 31 observed astronauts, were found to have a IJV diameter at the skull base of >1.55 cm, indicating significant right ventricular dilation relative to the left ventricle.

IJV cross-sectional area right/left ratio provides a pre-flight indicator of those who will not develop stasis. Additional data and analysis are needed to determine if the ratio can be used to predict those who will develop stasis.

Apixaban Safety and Efficacy for Prophylaxis and Treatment

NASA held a VTE working group in 2024 that recommended Apixaban as safe and effective treatment for detected in-flight clots (VTE Summary Report, 2025). Further evaluation by the external review panel has determined that it can also be beneficial when used at lower dose to prevent clot formation in individuals with higher risk physiology or known thrombosis risk factors.

The usual recommended treatment dose is 5 mg orally twice daily in patients with at least 2 of the following characteristics: age >80 years, body weight <60 kg, or serum creatinine >1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily. Apixaban 2.5mg vs 5 mg dose effectiveness. NASA's recommended prophylactic dose for high-risk astronauts is 2.5 mg twice daily, with dosing starting on the 3rd day of flight or once the astronaut has acclimated to the microgravity environment as determined by the flight surgeon. A study comparing apixaban 2.5mg and 5mg for extended phase therapy to prevent recurrent VTE found no difference in risks of recurrent VTE and major bleeding between the two doses (DeRemer et al., 2022).

Risks of Apixaban Use

The most concerning side effects of Apixaban include bleeding in the stomach, intestines brain, and eyes, however this has been shown to have low occurrences, even in older populations or patients with more co-morbidities than would be expected to be seen in the astronaut population.

Bleeding risks defined (Schulman & Kearon, 2005):

- Major bleeding is a composite of five criteria: fatal bleeding, clinically overt bleeding with hemoglobin decrease >/= 20g/L in 24 hours, critical site bleeding, bleeding requiring invasive intervention, or bleeding requiring reversal agent administration.
- Clinically relevant non-major bleeding (CRNMB) – overt bleeding not meeting the criteria for major bleeding but requiring medical intervention, unscheduled contact with a physician, temporary interruption of study drug, pain, or impairment of daily activities.

Summary Table of Bleeding Risks Associated with Apixaban Use

Category	AMPLIFY-EXT	AVERROES	HI-PRO	ARISTOTLE
Number of participants	2,486 (2,482 analyzed	5,599	600 total	18,201 randomized
Age of participants	Mean age 57	Mean age 70	Mean age 59.5	<65, 65-74, ≥75
Dose of Apixaban	2.5mg & 5mg BID	5mg BID	2.5mg BID	5mg BID (2.5mg subset)
Incidence of VTE	1.7% both doses	1.6% vs. 3.7%	1.3% vs. 10%	Not applicable
Major bleeding	0.2% vs. 0.1%	1.4% vs. 1.2%	0.3% vs. 0%	2.13%/yr vs. 3.09%/yar
Non-major bleeding	3.0% & 4.2%	3.1% vs. 2.7%	4.8% vs. 1.7%	Lower vs. Warfarin

Summary (key findings)	Both 2.5mg and 5mg BID reduced recurrent VTE (~1.7%) vs. placebo (8.8%) without increased major bleeding, CRNMB 3.0% & 4.2%	Apixaban reduced risk of stroke or systemic (1.6% vs. 3.7%) embolism without significantly increasing risk of major bleeding or intracranial hemorrhage	2.5mg BID lowered recurrent VTE (1.3% vs. 10%) with very low major bleeding; CRNMB 4.8% vs. 1.7% (NS)	AF trial: 5mg BID superior to Warfarin for stroke/systemic embolism, decreased major bleeding (2.13%/yr vs. 3.09%/yr) & intracranial hemorrhage
References: AMPLIFY-EXT (Agnelli et al., 2013); AVERROES (Connolly et al., 2011); HI-PRO (Pfeferman et al., 2026); ARISTOTLE (Granger et al., 2011)				

The overall risk of major bleeding associated with Apixaban use is approximately 1.4%/year (Connolly et al., 2011).

Apixaban Versus Aspirin for VTE Prevention

Apixaban provides substantially better VTE recurrence prevention than aspirin while carrying comparable bleeding risk. The AVERROES trial of 5,500 atrial fibrillation patients, unsuitable to take Warfarin, compared Apixaban vs. aspirin to determine efficacy with stroke or systemic embolism occurrence. The trial concluded early based on treatment benefit in favor of Apixaban (Connolly et al., 2011). The EINSTEIN CHOICE trial also supported the superiority of DOAC (rivaroxaban) versus aspirin in preventing VTE reoccurrence without significant increase in bleeding rates (Weitz et al., 2017).

Table 3. Rates of Study Outcomes in the Two Treatment Groups.*

Outcome	Apixaban (N=2808)		Aspirin (N=2791)		Hazard Ratio with Apixaban (95% CI)	P Value
	no. of patients with first event	%/yr	*no. of patients with first event*	%/yr		
Stroke or systemic embolism	51	1.6	113	3.7	0.45 (0.32–0.62)	<0.001
Stroke, systemic embolism, or death	143	4.6	223	7.2	0.64 (0.51–0.78)	<0.001
Stroke, systemic embolism, myocardial infarction or death from vascular cause	132	4.2	197	6.4	0.66 (0.53–0.83)	<0.001
Stroke, systemic embolism, myocardial infarction, death from vascular cause, or major bleeding event	163	5.3	220	7.2	0.74 (0.60–0.90)	0.003
Stroke†	49	1.6	105	3.4	0.46 (0.33–0.65)	<0.001
Ischemic	35	1.1	93	3.0	0.37 (0.25–0.55)	<0.001
Hemorrhagic	6	0.2	9	0.3	0.67 (0.24–1.88)	0.45
Unspecified	9	0.3	4	0.1	2.24 (0.69–7.27)	0.18
Disabling or fatal	31	1.0	72	2.3	0.43 (0.28–0.65)	<0.001
Systemic embolism	2	0.1	13	0.4	0.15 (0.03–0.68)	0.01
Myocardial infarction	24	0.8	28	0.9	0.86 (0.50–1.48)	0.59
Death						
From any cause	111	3.5	140	4.4	0.79 (0.62–1.02)	0.07
From vascular cause	84	2.7	96	3.1	0.87 (0.65–1.17)	0.37
Hospitalization for cardiovascular cause	367	12.6	455	15.9	0.79 (0.69–0.91)	<0.001
Bleeding event						
Major	44	1.4	39	1.2	1.13 (0.74–1.75)	0.57
Intracranial	11	0.4	13	0.4	0.85 (0.38–1.90)	0.69
Subdural‡	4	0.1	2	0.1	—	—
Other intracranial, excluding hemorrhagic stroke and subdural‡	1	<0.1	2	0.1	—	—
Extracranial or unclassified	33	1.1	27	0.9	1.23 (0.74–2.05)	0.42
Gastrointestinal	12	0.4	14	0.4	0.86 (0.40–1.86)	0.71
Non-gastrointestinal	20	0.6	13	0.4	1.55 (0.77–3.12)	0.22
Fatal§	4	0.1	6	0.2	0.67 (0.19–2.37)	0.53
Clinically relevant nonmajor	96	3.1	84	2.7	1.15 (0.86–1.54)	0.35
Minor	188	6.3	153	5.0	1.24 (1.00–1.53)	0.05

* The percent per year is the rate per 100 patient-years of follow-up. All analyses were based on the time to a first event; patients could have more than one event.
† Stroke included ischemic and hemorrhagic (i.e., primary intracerebral bleeding) types; some strokes could not be classified (unspecified). Hemorrhagic stroke is also included in the categories of major bleeding and intracranial bleeding. Disabling or fatal stroke was defined by a modified Rankin score of 3 to 6. The modified Rankin score is a measure of the severity of stroke on a scale from 0 (no symptoms or disability) to 6 (death).
‡ Hazard ratios and P values were not calculated for these events because there were so few events.
§ Bleeding events were reported as fatal by the investigator and were confirmed at adjudication.

Source: Connolly et al., 2011

Use of Apixaban During Extra Vehicular Activities (EVAs)

One expressed concern regarding astronaut preventive use of Apixaban was that EVAs, including wearing of the very heavy EVA suits, pose very physical challenges and increased risk of bleeding-associated injury that could be worsened by Apixaban use.

Historically, breaks in treatment with an anticoagulant, as would be required for an EVA, were thought to be risky as hypercoagulability has been a known risk associated with discontinued anticoagulant treatment (Cundiff, 2008). This landscape has changed with the addition of more easily managed DOAC medications. Recent studies have shown that DOAC medications like Apixaban have fast onset and clearance and can be safely interrupted if they are managed correctly. Following oral dosing of DOACS, therapeutic anticoagulation is achieved quickly (with peak activity within 1-4 hours), and the drugs are cleared rapidly with a half-life of 7-14 hours (Berkowitz & Moll, 2017). Competitive athletes playing contact sports and taking anticoagulants have a similar risk and have found successful ways to manage the risk. Berkowitz & Moll describe personalized pharmacokinetic/pharmacodynamic (PK/PD) studies which aids patient-specific management by determining individuals' drug elimination half-life and plasma drug concentration levels to minimize bleeding risk.

Thus, astronauts will discontinue prophylactic Apixaban 24 hours prior to conducting high-risk extravehicular activities (EVAs) or based on individual Apixaban PK/PD study administration plan and will restart medication upon EVA completion. Additionally, astronauts will discontinue Apixaban use 48 hours prior to landing due to risks associated with the dynamic environment and high acceleration loads experienced during landing events.

Association of Altered Blood Flow and Risk of VTE

The previous Stasis sections in this document, as well as the 2025 VTE Summary Report describe in detail the attributes of abnormal blood flow and the grading system developed to classify flow via in-flight ultrasound, and the potential role in risk of developing VTE during spaceflight. The external review panel agreed that current definitions of stasis/slow flow via ultrasound imaging in-flight, grading criteria, and surveillance methods and frequency (pre- and in-flight) should be reviewed for further refinement. The following areas were proposed as potential pathways to further investigate for the relationship between observed hemodynamics in spaceflight and VTE risk:

- From a mechanistic perspective, these events align with Virchow's triad, but with a dominant contribution from altered flow rather than systemic hypercoagulability. Cephalad fluid shift in microgravity reduces hydrostatic gradients and contributes,

with other factors, to impaired venous drainage, including reduced or reversed jugular flow, consistent with venous stasis (Kim et al., 2021).

- Additional contributors may include endothelial alterations and mild procoagulant changes, but current evidence supports a model in which the hemodynamic component is central.
- Intracranial compliance (ICC) and cerebrospinal fluid (CSF)–venous coupling may play a role in this process, supported by other clinical and radiological findings after spaceflight. Reduced compliance could impair outflow, thereby contributing to venous stasis and potentially also to Spaceflight Associated Neuro-ocular Syndrome (SANS)-related phenomena. It remains unclear whether such changes are primarily induced by microgravity or reflect inter-individual variability. At present, these factors are insufficiently characterized and there is no evidence that ICC independently modifies the efficacy or bleeding risk of systemic anticoagulation.
- Theories for central nervous system changes include cephalad fluid shifts, venous and lymphatic outflow obstruction, and mild continuous increases in intracranial pressure. There is a need for in-flight monitoring capability for ICP (Marshall-Goebel et al., 2016; Bateman & Bateman, 2024).
- The role of dominant right jugular veins, collateral venous pathways, and the impact of anatomical variations such as styloid process compression is noteworthy. It is recommended to review styloid process anatomy in the identified cases to assess for potential jugular vein compression and its relevance to venous outflow obstruction.
- What is the contribution of stasis to the pathogenesis of terrestrial venous thromboembolism? While cancer and other hypercoagulable states account for many cases, a substantial proportion is driven primarily by stasis (Akrivou et al., 2022). Almost all systemic embolization in atrial fibrillation, for example, is attributable to stasis and turbulent flow within the left atrial appendage (Paliwal et al., 2024).
- There is a need for more detailed and higher-resolution physiological data to better understand venous flow dynamics, intracranial pressure–volume relationships, and their interaction in microgravity. This may include more refined assessment of venous flow patterns (e.g., regional flow distribution and pulsatility), characterization of pressure dynamics within the jugular and intracranial venous systems, and improved understanding of CSF–venous coupling.

Addressing the Risks Associated with PFO and VTE

A patent foramen ovale (PFO) is a shunt between the right atrium and the left atrium of the heart, which is a persisting remnant of a physiological communication present in the fetal

heart. Post-natal increases in left atrial pressure usually force the inter-septal valve against the septum secundum and within the first 2 years of life, the septae permanently fuse due to the development of fibrous adhesions (Saary & Gray, 2001). Thus, all humans are born with a PFO and approximately 75% of PFOs fuse following childbirth (Steiner et al., 1998). For the 25% of the population's whose PFOs do not fuse, ~6% have what is considered by some to be a large PFO (> 2 mm). PFO diameter can increase with age (Hagen, Scholz, & Edwards, 1984).

Cephalad fluid shift in microgravity is associated with multiple cardiovascular adaptations, most notably increased cardiac preload and central venous return (Stepanek, Blue, & Parazynski, 2019; Norsk, 2020). Several hemodynamic consequences may influence PFO physiology, including:

- Increased right atrial filling and transmural venous pressure, promoting right-to-left shunting (Norsk, 2020)
- Thrombus formation that could serve as a source of paradoxical emboli (Kim et al., 2021; Aunon-Chancellor et al., 2020)
- Hemoconcentration from diuresis-mediated plasma volume reduction, along with endothelial changes (Goswami et al., 2025; Krittanawong et al., 2023)

Although no paradoxical embolic events have been reported in astronauts, this mechanism is directly relevant to risk discussions for PFO-positive astronauts. The clinical relevance of increased risk of VTE in astronauts with PFO is being considered and will be the topic of a future working group.

Addressing the Association Between SANS and VTE

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 to date

on the relationship between SANS and VTE do not show a correlation (NASA HRP, 2022a; NASA HRP, 2022b).

Defining Stasis/Slow Flow via Ultrasound and Other Imaging/Surveillance

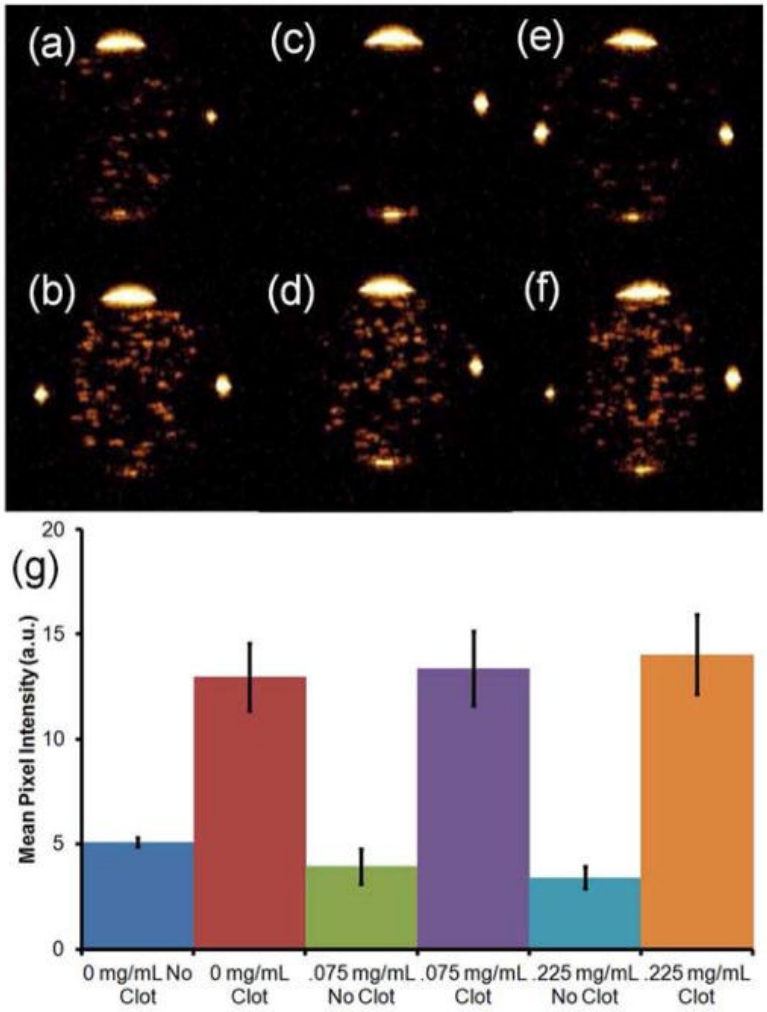
Current Use of Ultrasound to Evaluate Astronaut Blood Flow

Current protocol to evaluate active NASA astronauts includes ultrasound (US) of the deep veins to establish an 'Earth-based terrestrial baseline', collected with the subject's head and torso elevation not exceeding 10 degrees from horizontal. In-flight duplex US of the bilateral internal jugular veins are collected at 30- and 60-days post-launch, and 6 weeks prior to return to Earth. Additional US are collected in-flight if abnormalities are identified. Terrestrial US exams use machine setting of 'upper extremity venous', and in-flight exams are completed in either the 'upper extremity venous' or a customized 'small part' preset. Additional information on the NASA occupational surveillance program to evaluate astronauts for venous thrombosis can be found in Pavela et al. (2022).

As identified by a systematic review of the use of ultrasound for venous assessment in spaceflight (Elias et al., 2024), in-flight US equipment should include high resolution imaging devices and scanners with various US emissions frequencies in B-mode and adequate transducer sizes in order to be comparable to terrestrial standards. Additionally, it is suggested to integrate different US modalities, i.e., B-mode + color-flow + doppler US for optimal venous assessment. The review also describes the increased complexity of upper extremity thrombosis screening in space compared to US limited to the jugular veins or lower-limb peripheral veins, which can be performed more accurately by an operator with limited training. The potential location of a thrombus may concern isolated central (i.e., intrathoracic) or deep IJV, requiring more advanced imaging modalities. As thrombus have been identified in the sigmoid/transverse sinus (see section entitled Cerebral Venous Aspects of Clots), there is a need for additional screening capability in-flight beyond the current utilized US.

Alternatives to the Current Ultrasound Protocol

One potential alternative to current US is to utilize Contrast-Enhanced Ultrasound (CEUS) through the combination of US with intravenously injected gas filled bubbles to further enhance the quality of US images (Blomley et al., 2001). CEUS using microbubbles has been found to improve imaging by allowing real-time high-resolution visualization of blood flow, microvascular perfusion, and improved visualization of deep vein thrombosis (Abou Ali et al., 2025). Further investigation into the contrast agent utilized has improved identification of smaller, acute, non-occlusive clots, with the use of targeted thrombin-activated microbubbles (Nakatsuka et al., 2013; Lux et al., 2017; Wang et al., 2021).



Static Contrast Enhanced Ultrasound Imaging: TACS crosslinked microbubbles with 0 mg/mL PEG loading in non-clotting (a) and actively-clotting blood (b), bubbles with .075 mg/mL PEG loading in non-clotting (c) and actively-clotting blood (d), and bubbles with .225 mg/mL PEG loading in non-clotting (e) and actively-clotting blood (f).(g) Average of three brightness analyses within the respective phantoms, error bars are the 95% confidence interval. *Source:* *Nakatsuka et al., 2013*

Considerations of the spaceflight environment must be taken into account if implementing CEUS imaging, such as potential alterations to the reaction of the microbubbles in microgravity in combination with the observed physiological changes in fluid shifts, blood volume, and vessel changes that occur in-flight. Additionally, microbubble agents are inherently unstable and maintaining the integrity requires special storage considerations. The injected microbubbles also dissolve or clear from the body within minutes, allowing a short diagnostic window that would require highly efficient coordination between the crew and terrestrially based medical teams.

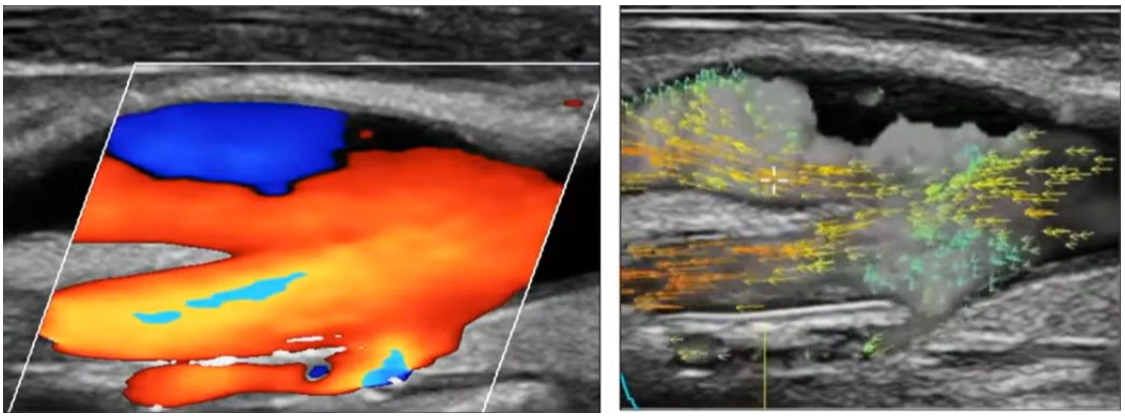
Another alternative imaging modality that is currently being explored is Vector Flow Imaging (VFI). VFI is an advanced high frame-rate US providing multi-dimensional, angle-independent estimation of flow velocity. It enables detailed dynamic visualization of complex hemodynamic states by showing even transient events that would be otherwise undetectable (Hansen et al., 2017; Goddi et al., 2017; Baun, 2021).

Conventional doppler ultrasound methods rely on operator-related angle variables that can create errors and variations in estimating blood flow velocity. Additionally, most contemporary US estimate blood flow volume using raw back-end data that can be affected by the wide variations in received doppler frequencies that occur due to spatial and temporal velocity variations within the region of interest. Further, through extensive in vitro and in vivo studies, it has been established that blood flow in cylindrical arterial conduits is a complex 3D phenomenon that creates velocity variations in the cardiac cycle and directional changes that cannot be captured with conventional diagnostic US methods (Baun, 2021). Conversely, VFI permits real-time assessment through 3D flow geometry and absolute velocity values within the targeted region. VFI uses multiple acoustic wavefronts transmitted at varying angles to quantify hemodynamic information, including direction and flow velocities, complex flow, and wall shear rate quantification. The received data are stored in channel domain memory and analyzed using proprietary software algorithms to plot flow variables at defined points within individual micro streams and displayed visually as color-coded flow vectors. The provided VFI images are interpretated using the following three factors:

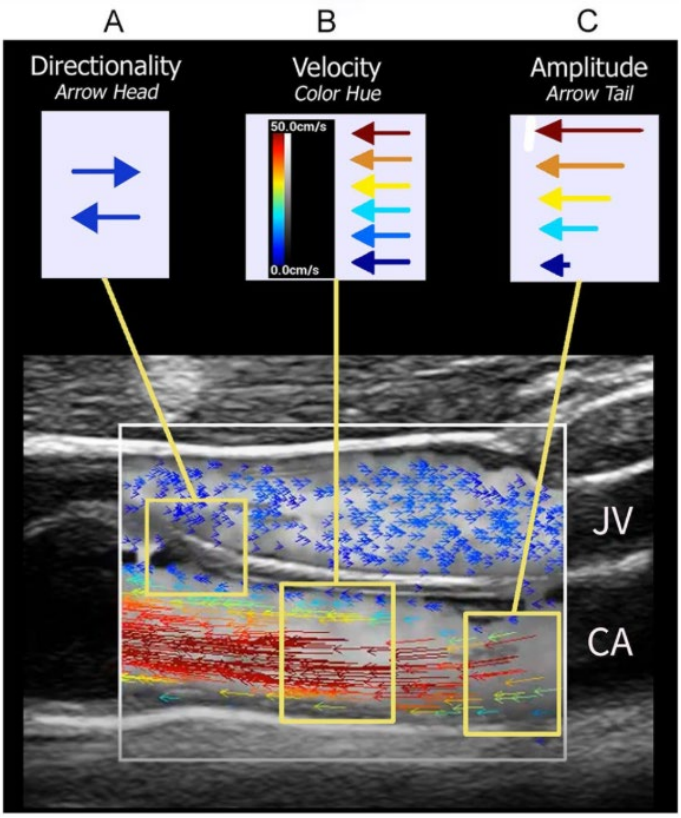
1) Velocity: Color hue represents velocity at a specific point within the micro stream and is not related to flow direction.
2) Directionality: Flow direction, either away or toward the transducer, is represented by arrowheads at either end of the vector line.
3) Magnitude: The amplitude of flow represented the concentration of speckle scatters present at each discrete vector point, representing the magnitude the volume of blood coursing along each sampled location within the micro stream.

In the produced VFI images, the green arrows represent low velocity, yellow arrows represent medium velocity, red arrows represent high velocity, and longer arrow length represents faster blood flow.

Duplex Ultrasound (left) compared to VFI (right)



From: Vector Flow Imaging explained by Dr. Goddi (YouTube)



Longitudinal image through the carotid artery (CA) and jugular vein (JV) captured during systole demonstrating hemodynamic variables represented by ultrasound vector flow imaging. (A) Flow directionality: Direction of arrowhead indicates direction of flow relative to transducer placement. Note blue arrowheads in JV are pointing to the right indicating flow toward the patient's feet, while blue arrowhead in the CA are pointing to the left indicating flow toward the patient's head. (B) Flow velocity: Color hue of each vector indicates absolute flow velocity determined by speckle tracking methods. In this example,

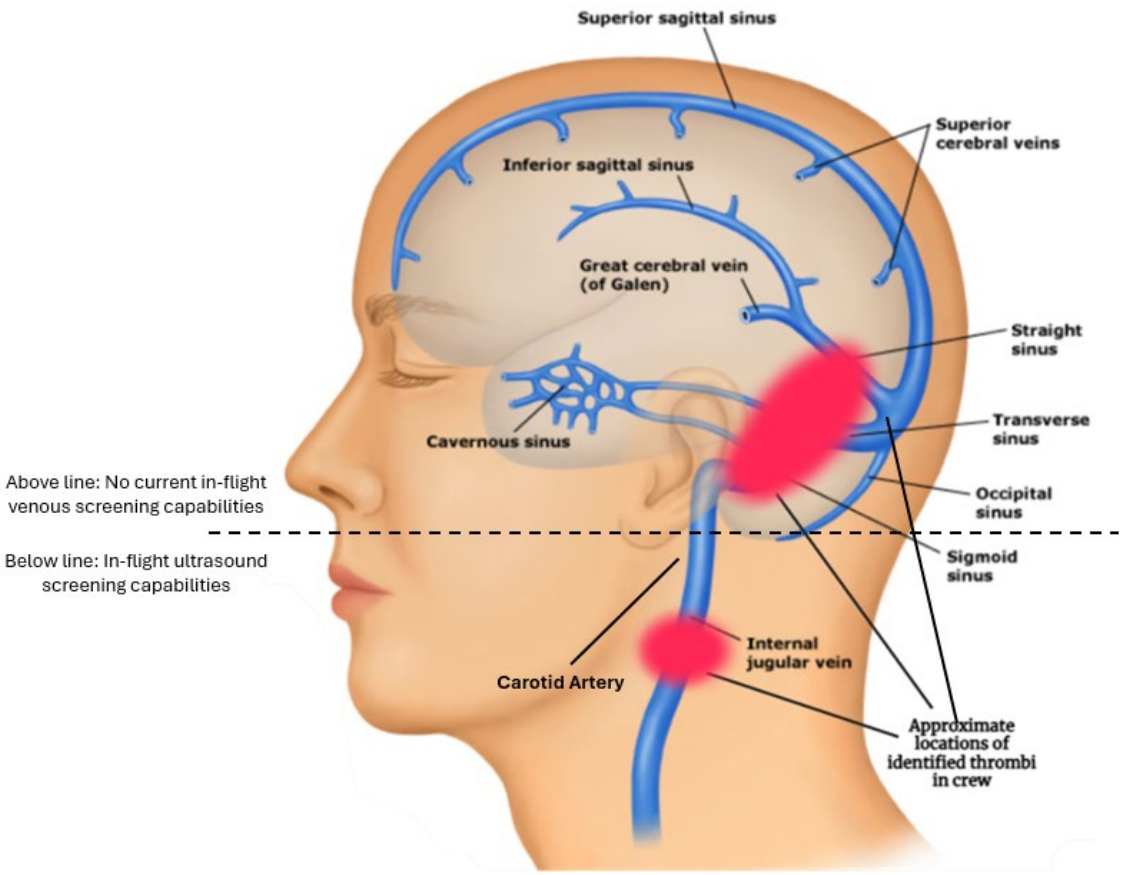
slower arterial flow (blue) is observed adjacent to the intimal surface with increasing velocities (dark red) mapped toward the center of the bloodstream during systole. (C) Amplitude: Concentration (volume) of scatterers at each vector location is indicated by arrow tail length. As one would expect, a greater volume of blood is coursing through the center of the stream during systole. Compare tail lengths of red vectors with blue vectors; longer tail lengths in center of stream versus shorter tail lengths near vessel wall. *From: Baun, 2021*

One factor to consider for utilizing VFI in spaceflight is that due to the extensive amount of data collected to generate VFI images (up to 1,000 frames per second), there is a vast amount of data storage required in order to collect and process VFI scans completed in-flight. Transmitting the collected VFI images to terrestrial support for expert review and analysis would be greatly limited.

Capability to Assess Astronauts Beyond Jugular Veins

Jugular and cerebral thrombi have been identified within crewmembers on the International Space Station (ISS). One incidental finding located a compressible thrombosis in the left IJV, with the crewmember presenting without symptoms. Additional cases of incompressible thrombi have been found in the cerebral sinuses of astronauts, specifically the sigmoid/transverse sinus. The presenting cases experienced symptoms in-flight, including persistent headache, eyelid swelling, facial edema and nasal congestion, hearing loss, left facial asymmetry, strength/grip asymmetry, and altered mental status, and swelling in the upper part of the left clavicle and posterior part of the sternocleidomastoid muscle.

Post-flight imaging of the cases identified thrombi in the sigmoid/transverse sinus, left-side torcular, and left IJV.



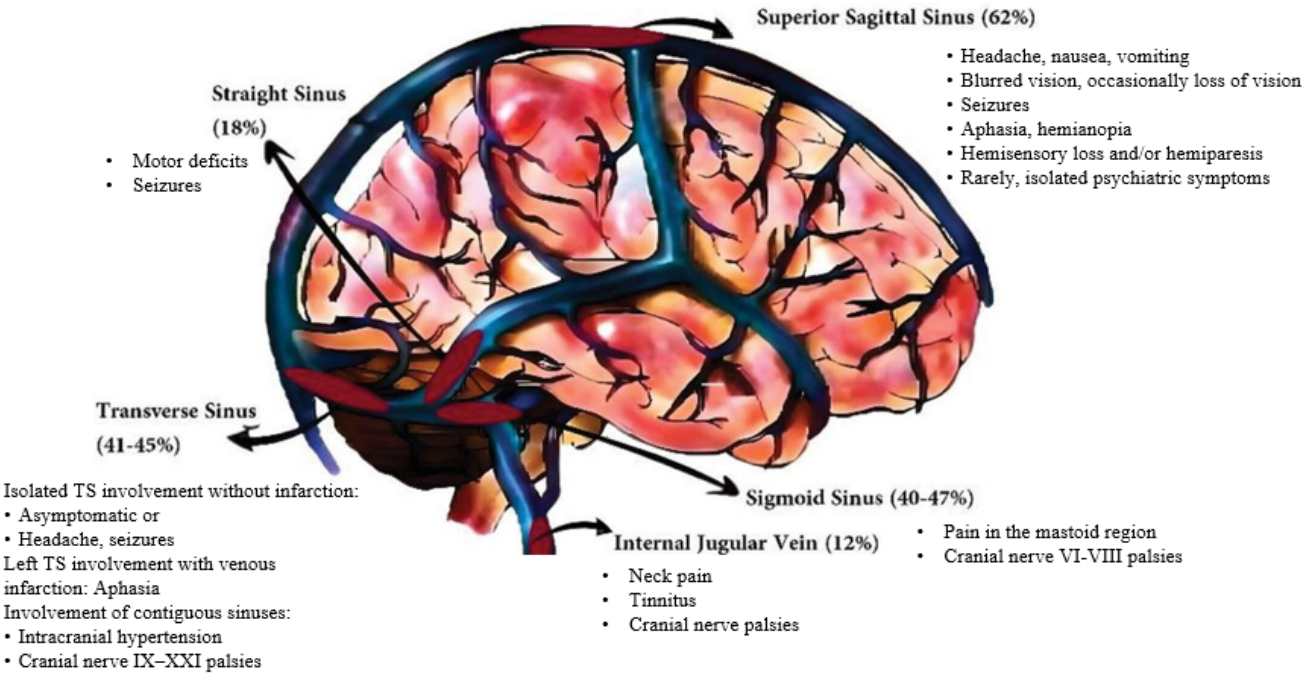
These findings of thrombi beyond the IJV into the cerebral sinuses highlight the urgent need for additional screening methodology that can be utilized in spaceflight to diagnose potential thrombi above the IJV. Terrestrially, cerebral sinus thrombi are typically diagnosed using an MRI combined with MR venography (MRV), or a CT venography (CTV). However, the limitations of mass and equipment capability in-flight will require alternatives to the terrestrial standard of care. One option postulated by the external review panel suggested the use of a transcranial doppler (TCD) to scan astronauts for potential cerebral sinus thrombi in-flight. TCD is non-invasive and can detect absent, markedly elevated, or reversed flow velocities in the cerebral sinuses, indicating obstruction. TCD is effective for tracking changes in venous hemodynamics over time and found to be an effective means of diagnosing transverse and straight sinus thrombi if there are no other neuroimaging modalities available. The inclusion of contrast with TCD, known as transcranial color-coded sonography (TCCS), can improve the detection rate of cerebral veins and sinuses with increased velocity values (Zhu et al., 2019; Pan et al., 2022). Limitations of using TCD include high dependency on the sonographer/operator skills, anatomic variability in individuals that makes interpretation challenging, and the overall lower sensitivity of diagnostic capability compared to MRI or CT.

Cerebral Venous Aspects of Clots

Symptomology of Cerebral Venous Sinus Thrombosis

Understanding the symptomology of cerebral venous sinus thrombosis (CVST) is an important aspect in identifying potential cases. The most common symptom, occurring in 80 to 90% of CVST patients, is headache, often exacerbated by the Valsalva maneuver or coughing which suggests elevated intracranial pressure (ICP). Papilledema and visual disturbances may accompany the headache as ICP rises significantly. Focal neurologic symptoms, such as motor weakness occurs in up to 44% of patients, and seizures in approximately 40% of patients with focal seizure being the most prevalent. Within those who develop seizures, 50% experience focal onset. The combination of headache with either focal neurologic deficit or new-onset seizure should prompt consideration of CVST (Singh, Munakomi, & Baruffi, 2025).

CVST symptom presentation can also vary based on location of the thrombosis within the cerebral venous sinus network. The graphic below displays the distribution of CVST in percentage along with the commonly associated symptoms for each thrombosis location.



Adapted from: Ranjan, Ken-Dror, & Sharma, 2023

CSVT symptoms when presented often resemble a transient ischemic attack or ischemic stroke (Singh, Munakomi, & Baruffi, 2025; Rivera et al., 2026). Differentiating between the two is important to determine the appropriate next treatment steps. While high-detailed imaging (such as MRI or CT) is the golden rule for identifying whether the presenting case is

a thrombosis versus a stroke, other clinical factors may lead to better determining the diagnosis. In one presented case study, the subacute history of persistent headache preceding a focal deficit was found to be a clue in that the patient was experiencing a CVST and not an acute ischemic stroke. The final recommendation was that when a headache precedes neurologic deficits and arterial imaging is unrevealing, CVST should remain a diagnostic consideration (Rivera et al., 2026). The expert review panel suggested the inclusion of an electroencephalogram (EEG) for in-flight assessment to rule out potential neurologic events when clinical symptomology arises.

Pre-Flight Assessments

Astronauts undergo an extensive list of medical testing performed pre-flight at varying time-points (OCHMO-STD-100.1a, 2024). To determine risk level for potential thrombosis events, astronauts receive a thrombophilia panel that screens for the following:

- Factor V Leiden heterozygous
- Factor V Leiden homozygous
- Factor V Leiden with other thrombophilia conditions like a prothrombin gene mutation
- Protein C deficiency
- Protein S deficiency
- Antithrombin III deficiency
- Prothrombin gene mutation, heterozygous
- Cardiolipin IgG Antibody
- B2 glycoprotein 1 IgM/IgG Antibody
- 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)

Additionally, history of unprovoked VTE (not superficial thrombophlebitis) in a first-degree family member and current use of higher-risk hormones (as defined in the 2025 VTE Summary Report Hormone Comparison Table on page 19) is established.

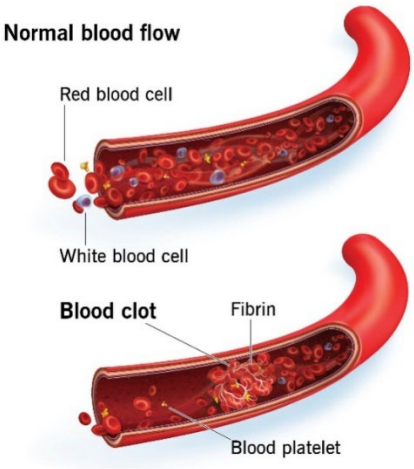
Finally, astronauts receive ultrasound imaging and MRV with contrast to establish baseline anatomy of the venous system.

The expert review panel suggested further investigation into the potential benefits of the following additional pre-flight screening to be added:

- 4D flow MRI sequence extended to the brachiocephalic trunk for in-depth analysis of complex hemodynamics in the carotid and subclavian vessels.
- MRI of the IJV with right to left ratio at the base of the skull to assess for potential asymmetry that may indicate IJV stenosis which may be associated with idiopathic intracranial hypertension and cerebral venous drainage obstruction.
- Styloid process evaluation to assess for elongation or ossification of the stylohyoid ligament, which may cause Eagle syndrome characterized by chronic throat or neck pain.
- A jugular valve competence assessment to evaluate venous pressure, flow anomalies, and anatomical variability in venous drainage.

D-dimer for In-Flight Risk Assessment

D-dimer is a small protein fragment produced when a blood clot is formed and then broken down by body's fibrinolytic system. D-dimer levels can be detected in a simple blood test and can give surveillance information when a blood clot (i.e., DVT, PE, or VTE) is suspected (Clevland Clinic, 2021).



Source: Clevland Clinic, 2021

Sensitivity and Specificity

D-dimer has high sensitivity (>95%) which makes it a very effective test to rule out thrombotic disorders. A negative D-dimer combined with a clinical assessment such as Wells test (below) can reduce need for CT scans or ultrasound and clinical probability can have a 99% negative predictive value for VTE (Pulivarthi & Gurram, 2014; van Es et al., 2016).

DVT likelihood interpretation

All items in the Wells score are awarded 1 point when positive, except for item 10 (intravenous drug use) which is awarded 3 points and item 11 (alternative diagnosis more likely than DVT) which subtracts 2 points from the score.

Therefore, the Wells scores range from – 2 to 12. The table below explains the risk groups proposed by the model and the diagnosis pathways:

Wells score	Interpretation	Pre test DVT probability	D-dimer	Ultrasound
<1	DVT unlikely	5% - low probability	negative	not necessary
<1	DVT unlikely	5% - low probability	positive	necessary
1 - 2	DVT unlikely	17% - moderate probability	negative	not necessary/necessary upon clinical decision
1 - 2	DVT unlikely	17% - moderate probability	positive	compulsory
>2	DVT likely	35% - high probability	negative	necessary
>2	DVT likely	35% - high probability	positive	compulsory

Sample implementation of D-dimer and Wells Score. Source: Wells et al., 2006; Silveira et al., 2015

D-dimer has low specificity (35-46%) therefore is not a good single diagnostic tool (Patel et al., 2020). High D-dimer levels are not only caused by clotting disorders but can be caused by many other health and inflammatory conditions including pregnancy, heart disease, arthritis, exercise, stress, age, and recent surgery, illness, or trauma (Franchini et al., 2023). It can be used as surveillance and when symptoms or other clinical indicators are present, D-dimer can help build the case that further testing/surveillance including additional imaging could be beneficial to identify a clotting disease process.

Normal/Reference Values

Normal terrestrial D-dimer levels have a wide range and can vary greatly from person to person. Common lab reference ranges include <500 ng/ml, but can vary with age, health and activity conditions (Killeen & Kok, 2025).

D-dimer Testing in Spaceflight

NASA does not routinely test D-dimer levels in astronauts. There are no existing adequate in-flight testing methods, and it is considered an imprecise test not singularly adequate for clot diagnosis, but this practice may change. Within the past 6 years, multiple astronauts have experienced a clot-related event and NASA is looking for more indicators to assist with early clot detection.

The Canadian Space Agency (CSA) has been evaluating testing potential of D-dimer hardware for in-flight use. Some early limitations identified to flying D-dimer hardware

includes the requirement for cold stowage of cartridges and control samples with a 15-minute acclimation period before use, and a 12-18 month stability at room temperature.

CSA D-dimer hardware prepared for ISS tech demo study

Intervention and Treatment

More frequent surveillance may enable earlier clot detection. It is assumed that in-flight D-dimer, as terrestrially, can be elevated by factors other than clotting, therefore a substantial increase is required to initiate any intervention activity. Elevated levels, symptoms, and other risk factors may be present and considered to determine if additional imaging/testing is needed and what treatment approaches are appropriate. Depending on the overall picture, astronauts may receive preventive anticoagulant, treatment anticoagulant, or other treatment or surveillance necessary to ensure the safety of the astronaut and crew.

Expert Panel Conclusions

- The expert panel agreed that in-flight D-dimer could be helpful as a surveillance tool, allowing attention to be brought to a clot situation earlier and when used in conjunction with other information including imaging (in-flight US), symptoms, and known risk factors, can assist with clot diagnosis and monitoring.
- Pre-flight D-dimer testing was discussed but the panel concluded it is not likely healthy astronauts would show any elevation and clotting pre-flight, and it is not known at this time what influence the microgravity environment may have on D-dimer levels and testing methodology, making pre-flight testing an inadequate baseline measure.
- The panel suggested further investigation for future implementation to establish a baseline D-dimer level as early as possible in-flight (once fluid shifts settle) at approximately L+ 14 days and begin surveillance testing at L+30, with the need to consider additional test schedules to continue surveillance. Levels observed ≥60% increase from baseline level would lead to potential prophylactic Apixaban use, in combination with other risk factors.

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