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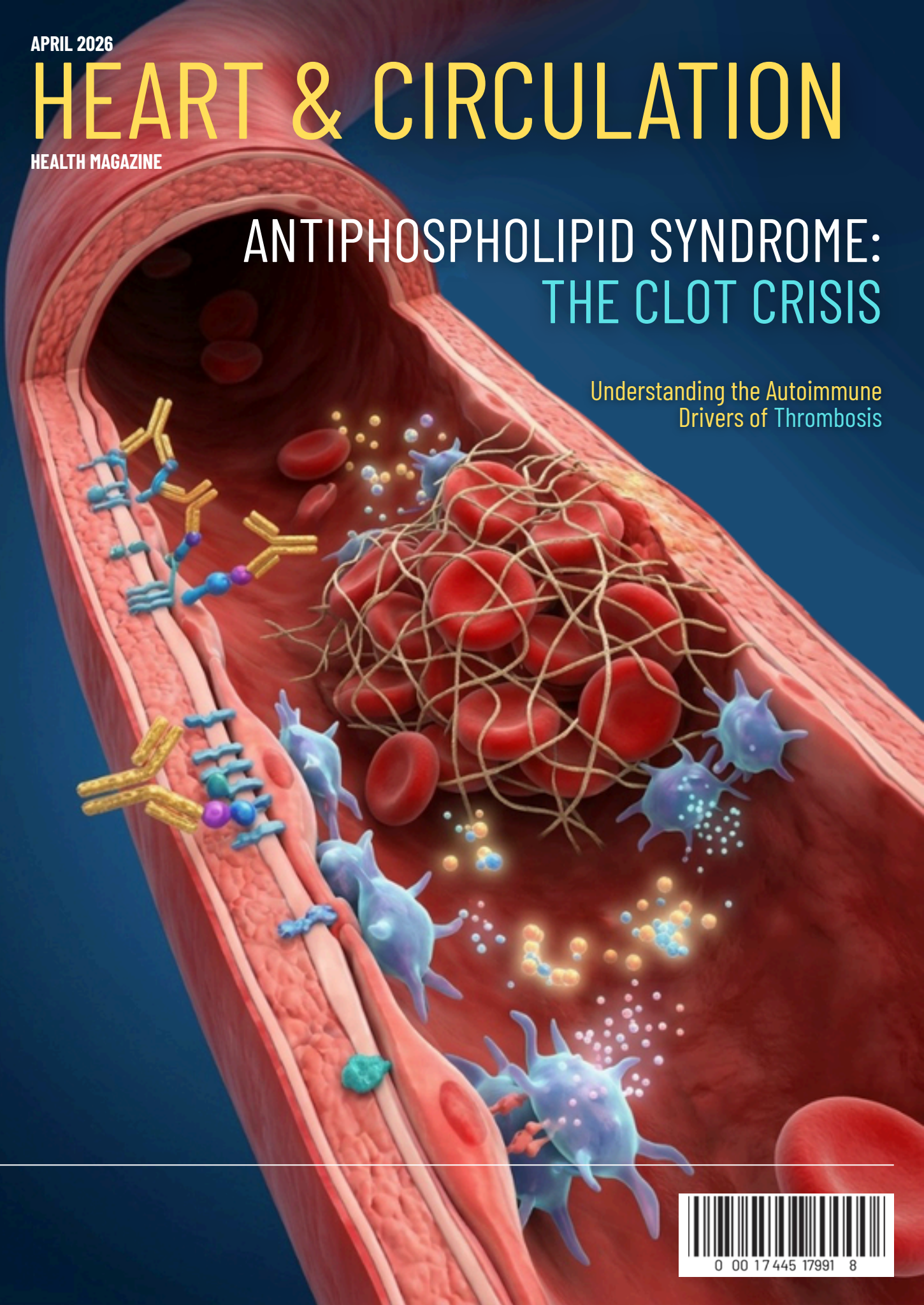
HEART & CIRCULATION

HEALTH MAGAZINE

ANTIPHOSPHOLIPID SYNDROME: THE CLOT CRISIS

Understanding the Autoimmune Drivers of Thrombosis



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THE TRAGIC CASE OF MAY STEWART, 22

A tragedy fate fell upon a healthy, young lady. The cause may, in fact, be found hidden deep within her body, in the genetic code itself...

Silent Clot: The Sudden Death of a 22-Year-old

It was just past 8 a.m. when May Stewart's roommate pushed open her bedroom door, expecting to find nothing but an empty hallway. Instead, she found May motionless in the bathroom — unresponsive, pale, and cold to the touch. Paramedics arrived within minutes, but by the time she reached the emergency room, May was pronounced **dead**.

What initially appeared to be an unexplainable tragedy soon revealed a far more convoluted cause—one that had been waiting in silence for years.[1]

Unraveling the Cause: A Clot Without a Warning

Initially, there was little to explain May's sudden death.

She had no signs of physical trauma. No history of drug use. No indication of acute infection or chronic diseases that can potential lead to her death. For an otherwise healthy 22-year-old, the absence of an immediate explanation is usually a sign of a rarer, less studied underlying condition.

The investigation began, as it often does, at **autopsy**.

The Culprit: Thrombosis

Upon examination of the brain, the hospital pathologist identified a critical finding: a **blockage in a major cerebral artery**, in which a major vessel had been occluded by a dense, fibrin-rich thrombus.

Surrounding brain tissue showed early signs of **ischemic injury**—cell death due to a prolonged depravation of oxygen. The pattern was consistent with an acute ischemic stroke, a critical condition that can lead to death within hours.

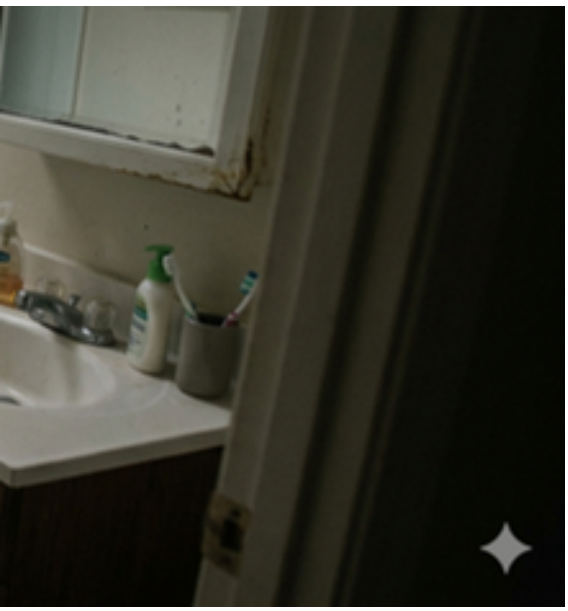
The pathologist ruled the death had been caused by a thrombus occluding vessels in the brain, leading to an ischemic stroke, quickly causing irreversible damage to the brain.[1]

BUT.....

WHY** did an otherwise health 22-year-old develop a thrombosis **so suddenly

Microscopic Findings

Autopsy found a network of fibrin interwoven with aggregated platelets, a hallmark of **hyperactive coagulation**, in which a patient's blood has an abnormally high tendency to clot.



> The mortality of a patient living with APS over 5 years was 5.3%. Of these, over 40% of deaths were due to **serious thrombotic events** such as: myocardial infarction, stroke and pulmonary embolism.[2]

> **Antiphospholipid Syndrome** may be a rare condition. It is not, however, a benign one.

Hyperactive Coagulation, a System in Overdrive

Postmortem blood testing detected the presence of **antiphospholipid antibodies**—immune proteins known to target phospholipid-binding proteins such as β2-glycoprotein I. These antibodies are one of the defining features of **Antiphospholipid Syndrome (APS)**.

> **APS:** an **autoimmune disorder causing blood clots**. It is a serious condition where **antibodies mistakenly attack phospholipids**, increasing **thrombosis risk**.

The Final Diagnosis

May Stewart's cause of death is a case of acute ischemic stroke due to arterial thrombosis, although the underlying cause is her Antiphospholipid Syndrome (APS).

What made May Stewart's case so tragic is the invisibility of the pathology. **APS is a silent until it presents itself, often in deadly ways.** It does not announce itself readily, and often, **patients will experience one or more unexpected thrombosis before they ever become aware of their underlying condition.**

There were often no immediate warning signs—only the silent formation of clots. And the silence, is often deadly.

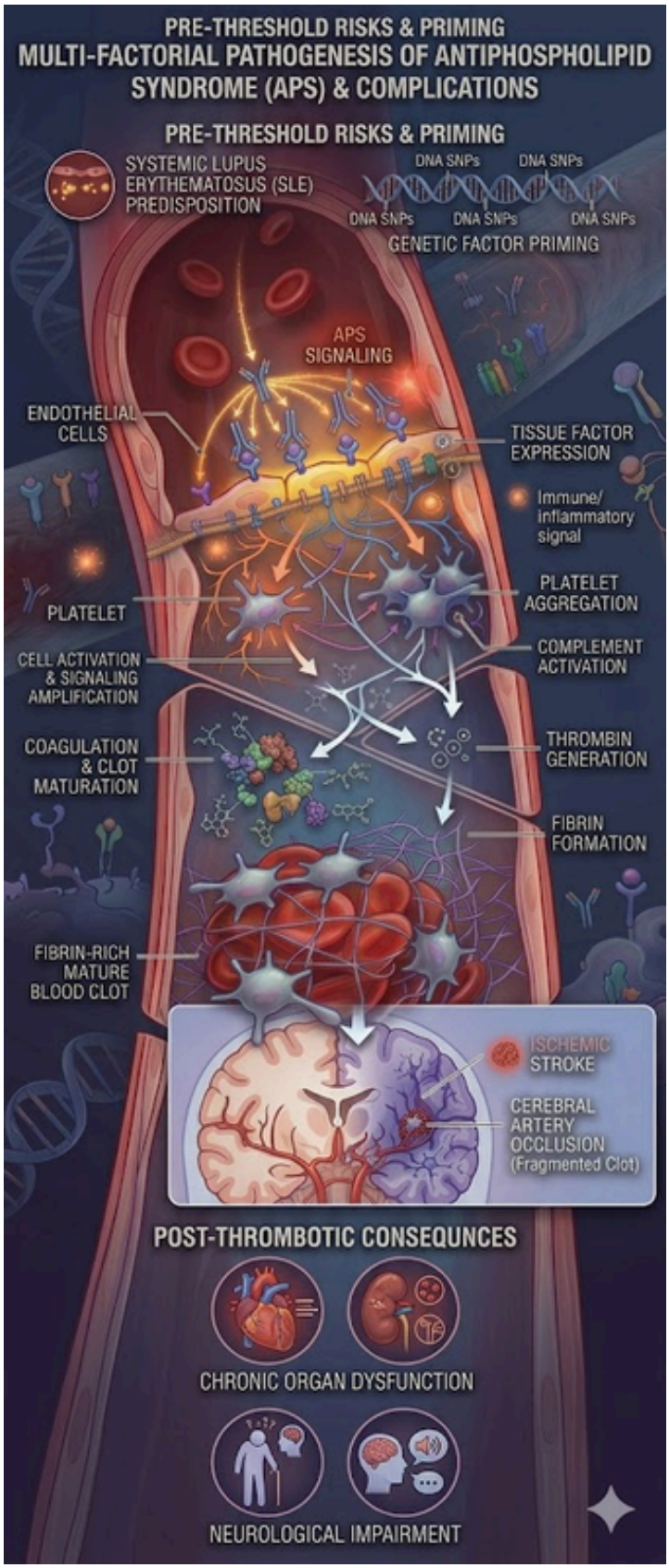
The investigation ended here. For May Stewart, it was too late. However, for many who carry APS antibodies in their bodies, hope is not lost. There are many prevention and management methods available to patients, but it is paramount that patients know this condition exists and is mindful of its potential consequences.[1]

Pathogenesis of APS-Induced Thrombosis

In Antiphospholipid Syndrome (APS), the body's immune system mistakenly produces antibodies that target proteins bound to phospholipids on cell membranes, particularly a protein called B2-glycoprotein I [3]. These antibodies attach to the surfaces of endothelial cells lining the blood vessels and to the circulating platelets, triggering signals that make these cells more likely to promote clotting, leading to increased expression of tissue factor, activation of platelets, and stimulation of inflammatory pathways that enhance the coagulation cascade[3]. As a result, the coagulation cascade is activated more easily and fibrin-rich clots can form inside blood vessels.

Several cellular players are central to this process. Endothelial cells, normally responsible for maintaining smooth blood flow, respond to antibody binding by expressing tissue factor, reducing anticoagulant proteins, and increasing adhesion molecules that attract platelets and immune cells. Meanwhile, platelets become activated, aggregate more readily, and release procoagulant substances that further amplify clot formation. The coagulation cascade itself is then intensified, as tissue factor promotes thrombin generation, which converts fibrinogen into fibrin, stabilizing the clot. In addition, complement activation contributes to local inflammation, which can damage tissues such as the placenta and lead to complications including placental thrombosis and recurrent miscarriage[3].

These clots may remain where they form or break loose and travel through the bloodstream. If one becomes lodged in an artery supplying the brain, it can block the flow of oxygen-rich blood and cause ischemic stroke[3].



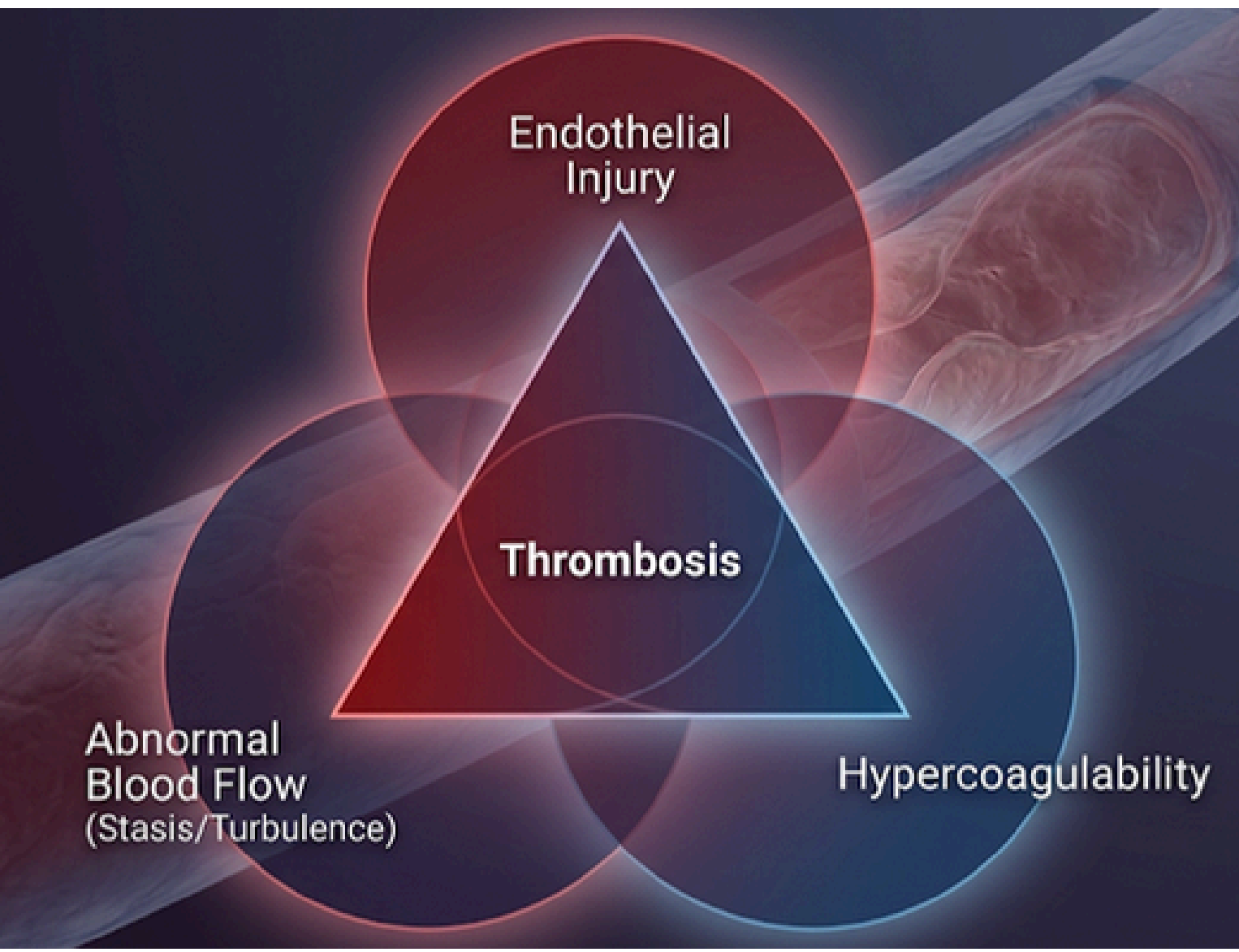
Virchow's Triad:
The 3 Forces Behind Thrombosis

HOW BLOOD CLOTS FORM AND WHY IT MATTERS

Long before modern imaging and molecular biology, physicians were already trying to understand why thrombosis occurs. In the 19th century, German pathologist Rudolf Virchow proposed a framework that is still used today, known as Virchow's triad [4].

Virchow suggested that blood clot arises from three major disturbances in the body's normal circulation: damage to the blood vessel wall (endothelium), abnormal blood flow, and an increased tendency of the blood to clot.

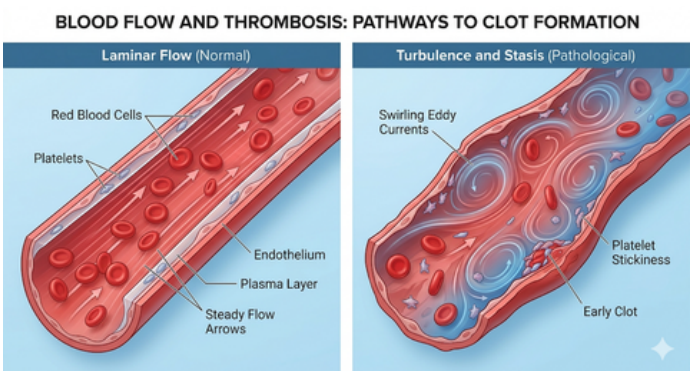
Each of these factors disrupts the balance that normally keeps blood fluid[4].



When blood flow slows down or becomes turbulent, clotting factors are no longer evenly distributed and can accumulate, increasing the chance of a clot forming. In laminar flow, red blood cells are centrally located and platelets remain separated from the endothelium by a plasma layer, which minimizes platelet activation and facilitates the dilution of clotting factors.

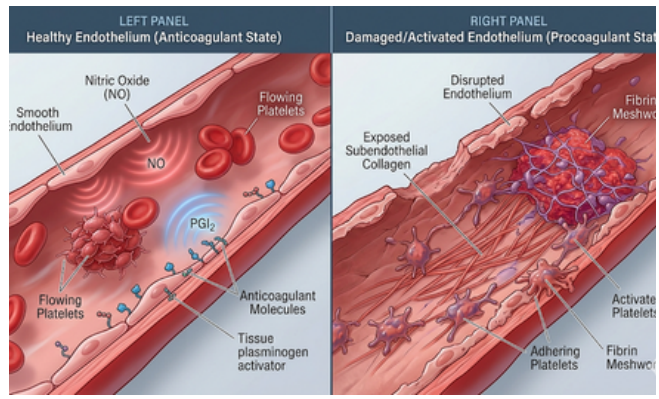
In contrast, turbulent flow generates eddy currents that increase shear stress, disrupt endothelial integrity, and increase the interactions between platelets and the vessel wall[5]. And stasis, or reduced blood flow, allows accumulation of activated clotting factors and reduces the inflow of anticoagulant substances, thereby favoring coagulation[5].

Both turbulence and stasis are considered pathological.



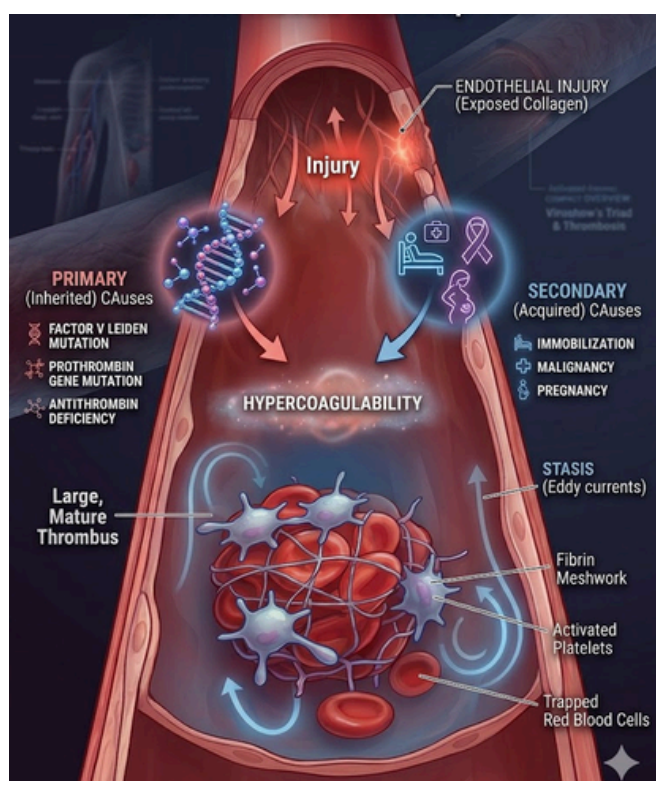
The endothelium normally maintains blood fluidity through the production of nitric oxide and prostacyclin, which inhibit platelet aggregation. It also expresses anticoagulant factors like heparin-like molecules and tissue plasminogen activator that promote fibrinolysis[6].

However, when endothelial cells are damaged or activated, this balance shifts toward a procoagulant state where the anticoagulant pathways are downregulated, thereby promoting platelet adhesion and activation of the coagulation cascade[6].



Finally, when the blood itself becomes more coagulable due to conditions like autoimmune disease, pregnancy, or genetic factors, the threshold for clot formation drops even further.

Hypercoagulability represents an increased intrinsic tendency of the blood to clot and may be primary or secondary in origin[7]. Primary causes include inherited defects such as Factor V Leiden mutation, prothrombin gene mutation, and deficiencies of protein C, protein S, or antithrombin, whereas secondary causes are more common and include conditions such as malignancy, immobilization, pregnancy, and autoimmune disorders, as well as antiphospholipid syndrome in our case study.



Symptoms of APS-related Thrombosis

Stroke[8]

- Dizziness
- Shortness of breath
- Pain from chest to arm

Heart Attack[9]

- Chest pain
- Dizzy
- Sweating
- Shortness of breath
- Pain from chest to arm

Deep Vein Thrombosis[10]

- Swelling and pain affecting 1 leg.
- Redness or warmth.

Pulomnary Embolism[9]

- Sudden shortness of breath.
- Chest pain.
- Coughing blood.

Pre-eclampsia[11]

- Severe headache
- Vision problems
- Sudden swelling of the face, hands or feet
- Pain just below the ribs

APS Complications

1. Recurrent fetal loss due to uteroplacental insufficiency [12]

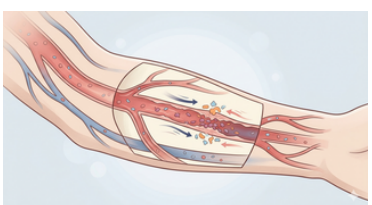
Cause 1: Placental thrombosis [12]
Clots formed in placental vessels, which reduce maternal blood flow to the placenta, causing fetal hypoxia.

Cause 2: Antiphospholipid antibodies targeting trophoblast cells[13]
Impairs trophoblast invasion into the uterine wall and decreases the active remodelling of the spiral arteries. The two abnormal processes can lead to shallow implantation of the placenta and decreased blood supply to the placenta, respectively. As a result, early pregnancy loss and spontaneous abortion often occurs.

Cause 3: Activation of the complement cascade[13]
leads to local inflammation of the placenta, causing placental tissue damage

2. Perioperative Thrombosis Risk

Perioperative Thrombosis Risk is defined as "thrombotic events occurring during or within 30 days of surgery". Surgical procedures inherently promote a prothrombotic state [14, 15], and this risk is significantly amplified in patients with APS, leading to Perioperative complications.



Venous stasis

Both anesthesia and postoperative immobility contribute to reduced blood flow. Anesthetic agents decrease venous return and induce vasodilation, leading to venous pooling.
This prolongs the contact time between platelets, clotting factors, and the endothelium, facilitating clot formation[14, 15]

Surgery exaggerates thrombosis risk following Virchow's triad

Endothelial injury

Tissue manipulation during surgery damages the vascular endothelium, promoting platelet adhesion and activation, which contributes to thrombus formation[14]

Hypercoagulability

Surgical stress triggers the release of catecholamines and cortisol, leading to increased coagulation factor levels, platelet activation, and reduced fibrinolysis[15]. In APS, where the baseline state is already hypercoagulable, this further shifts the balance toward clot formation[14].

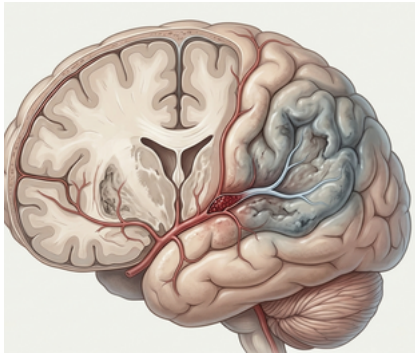
Anticoagulation strategies, like perioperative Heparin and Warfarin use, should be discussed and individualized prior to surgery in APS to balance the risks of thrombosis and bleeding[12].

Thrombosis Complications[12]

Ischemic stroke

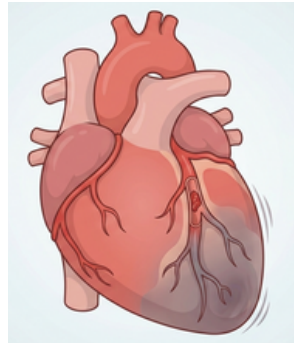
Thrombi blocks an artery supplying blood to the **brain**, causing hypoxia and brain cell death.

Complications include : cognitive dysfunction, deafness, blindness, etc.



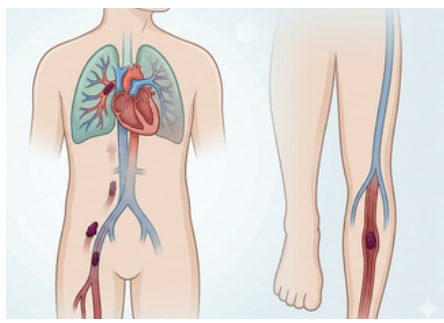
Acute coronary syndrome

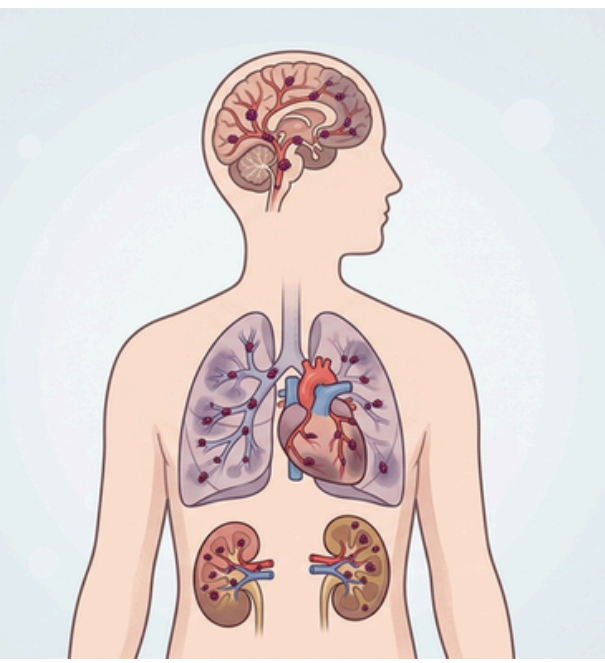
a sudden reduction of blood flow to the **heart** due to a thrombus blockage.



Pulmonary embolism and hypertension

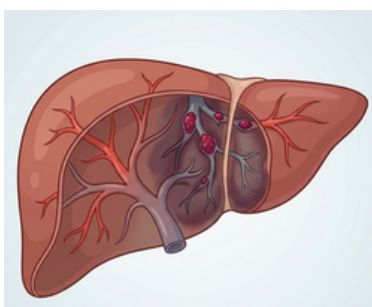
A thrombus travels from a vein in the lower limb to the pulmonary artery, causing a **pulmonary** embolism. This forces the heart to increase pressure, pumping blood through the narrowed, blocked blood vessel, thus causing pulmonary hypertension.





Catastrophic antiphospholipid syndrome (CAPS)

A life-threatening syndrome where thrombosis in small and medium-sized arteries of **multiple organs** over a few days.



Hepatic venoocclusive disease

Blocked sinusoids within the **liver**, causing injury and reduced blood flow

Mesenteric thrombosis

A blood flow blockage to the **intestines**, causing ischemia and necrosis

Skin ulcerations in lower extremities

Thrombosis of small dermal vessels, causing ischemia of **dermal tissue**, which leads to tissue necrosis and ulceration

Diagnosis

A patient must meet ≥1 criteria per category[12,16].

- **A History of:**
  - Vascular thrombosis
  - Pregnancy morbidity.

- **Presence of Antiphospholipid Antibodies[12,16]:**
  - Lupus anticoagulant
  - Anticardiolipin antibodies (IgG/IgM)
  - Anti-β2 glycoprotein I antibodies

For a valid result, lab tests must be positive on 2 separate occasions, ≥12 weeks apart. Transient positivity is indicative of **infection[12,16]**

Treatment

First-line treatment: anticoagulation[12,16]

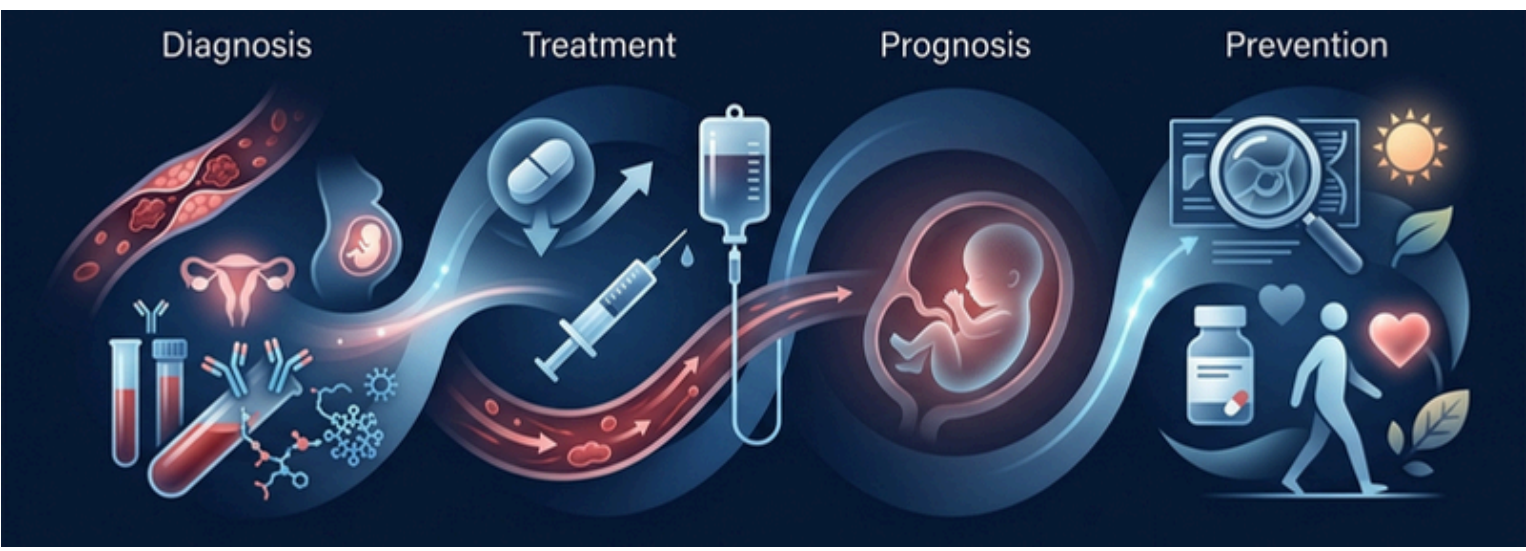
- Heparin (initial) → Warfarin (long-term)

Pregnancy management[12,16]

- Warfarin is not administered to pregnant women
- Low-dose aspirin + Heparin

Catastrophic Antiphospholipid Syndrome[12,16]

- Glucocorticoids, heparin, and plasma exchange



Prognosis

Mortality: ~6–10% at 10 years[12]

Morbidity: 30% develop permanent organ damage, and 20% develop severe disability[12]

Pregnancy morbidity:

- ≥ 1 unexplained pregnancy loss (≥ 10 weeks gestation)[12]
- ≥ 3 consecutive spontaneous abortions (< 10 weeks gestation)[12]
- ≥ 1 premature births (≤ 34th week gestation) due to placental insufficiencies[12]

Prevention

Primary prevention: [16]

- Screening for high-risk factors (i.e., lupus).
- High-risk patients are treated with low-dose aspirin[12]

Secondary Prevention (confirmed APS):[16]

- Prescribe anticoagulation drugs (i.e., Warfarin) to lower the risk of thrombosis.
- Managing a patient's lifestyle.
  - Stop smoking
  - Control blood pressure, cholesterol, diabetes, etc.

WORD SEARCH

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1. ANTIBODY
2. ANTICOAGULANT
3. ANTIPHOSPHOLIPID
4. AUTOIMMUNE
5. BLOOD
6. CIRCULATION
7. CLOT
8. DYSFUNCTION
9. EMBOLSIM
10. ENDOTHELIAL
11. FIBRIN
12. HYPERCOAGULABILITY
13. LAMINAR
14. LUPUS
15. OCCLUSION
16. PLATELET
17. STASIS
18. SYNDROME
19. THROMBOSIS
20. VIRCHOW

WORD SEARCH

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Be aware of your body.

Stay health.

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