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ILLUSTRATED REVIEW

Poststroke venous thromboembolism and neutrophil activation: an illustrated review

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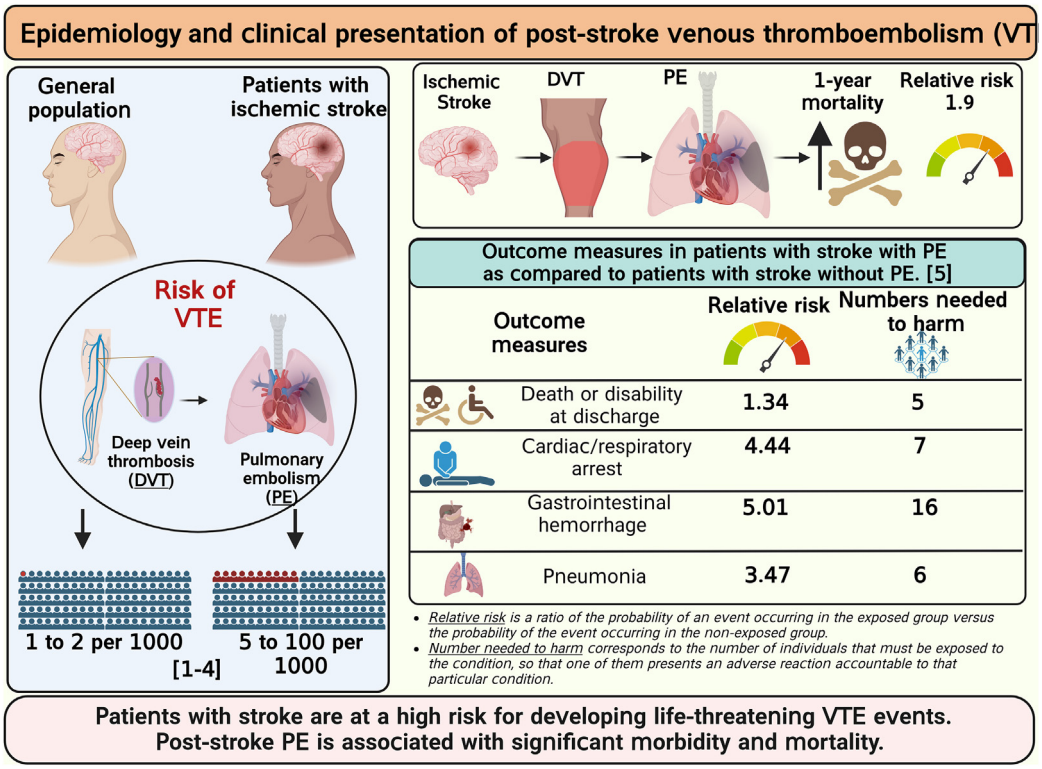
Abstract

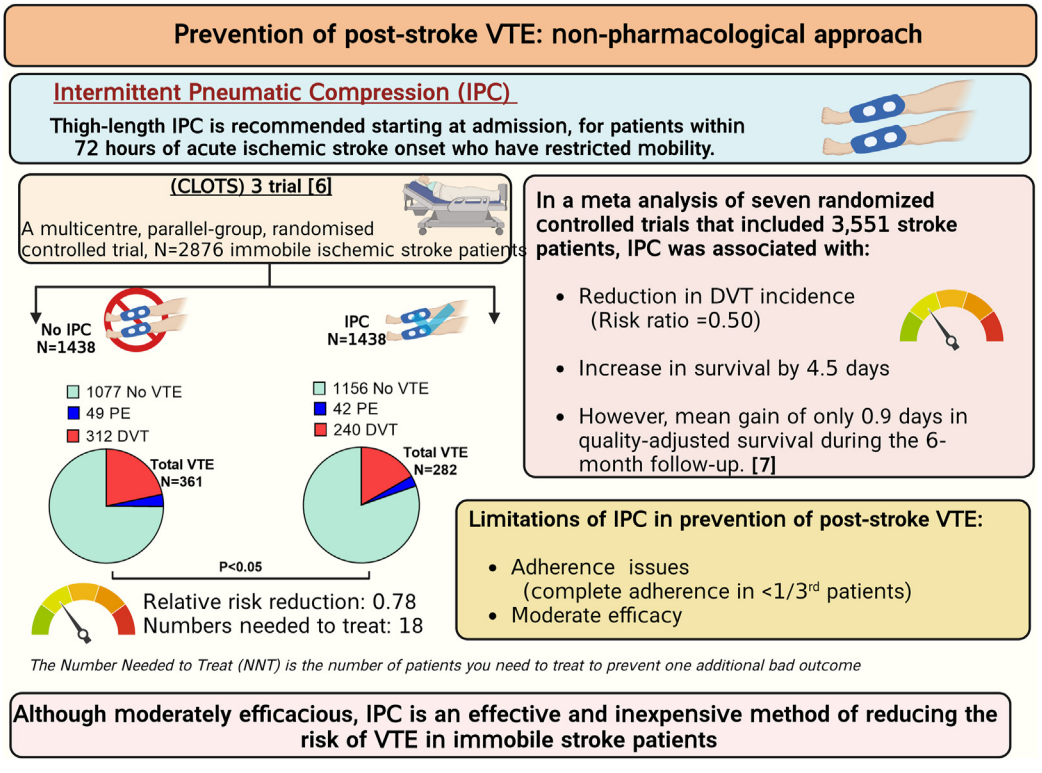
Patients with acute ischemic stroke are at a high risk of venous thromboembolism (VTE), such as deep vein thrombosis (DVT), estimated to affect approximately 80,000 patients with stroke each year in the United States. The prevalence of symptomatic DVT after acute stroke is approximately 10%. VTE is associated with increased rates of in-hospital death and disability, with higher prevalence of in-hospital complications and increased 1-year mortality in patients with stroke. Current guidelines recommend the use of pharmacologic VTE prophylaxis in patients with acute ischemic stroke. However, thromboprophylaxis prevents only half of expected VTE events and is associated with high risk of bleeding, suggesting the need for targeted alternative treatments to reduce VTE risk in these patients. Neutrophils are among the first cells in blood to respond after ischemic stroke. Importantly, coordinated interactions among neutrophils, platelets, and endothelial cells contribute to the development of DVT. In case of stroke and other related immune disorders, such as antiphospholipid syndrome, neutrophils potentiate thrombus propagation through the formation of neutrophil-platelet aggregates, secreting inflammatory mediators, complement activation, releasing tissue factor, and producing neutrophil extracellular traps. In this illustrated review article, we present epidemiology and management of poststroke VTE, preclinical and clinical evidence of neutrophil hyperactivation in stroke, and mechanisms for neutrophil-mediated VTE in the context of stroke. Given the hyperactivation of circulating neutrophils in patients with stroke, we propose that a better understanding of molecular mechanisms leading to neutrophil activation may result in the development of novel therapeutics to reduce the risk of VTE in this patient population.

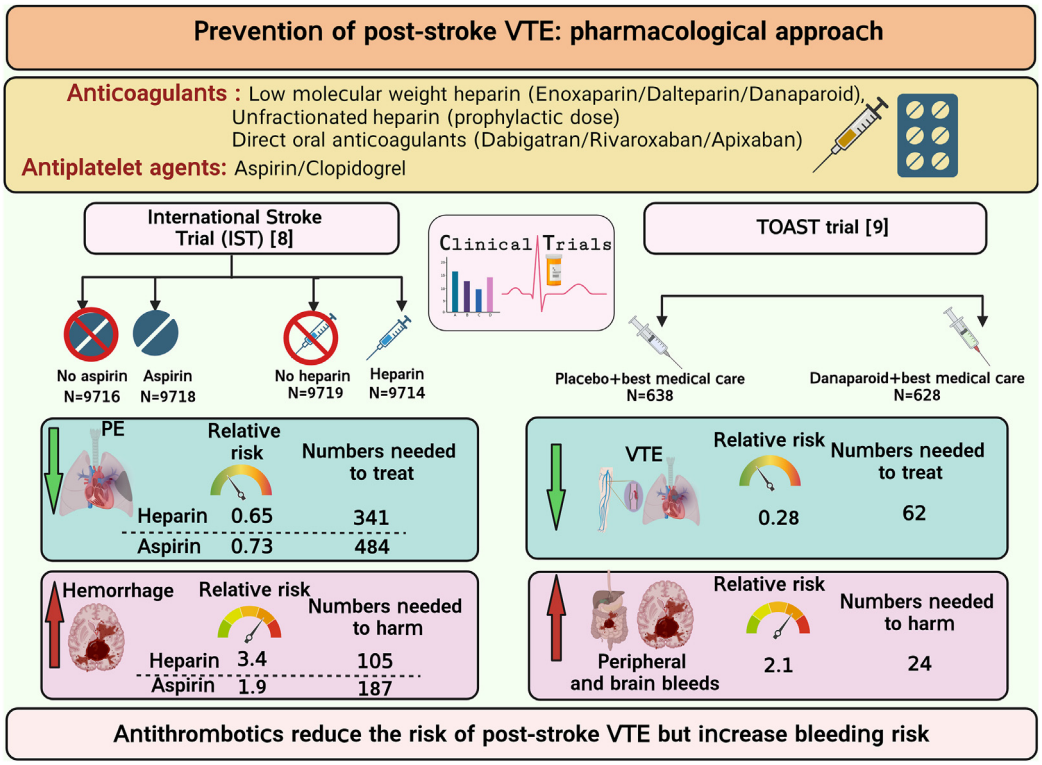
KEYWORDS
deep vein thrombosis, ischemic stroke, neutrophils, thromboprophylaxis, venous thromboembolism

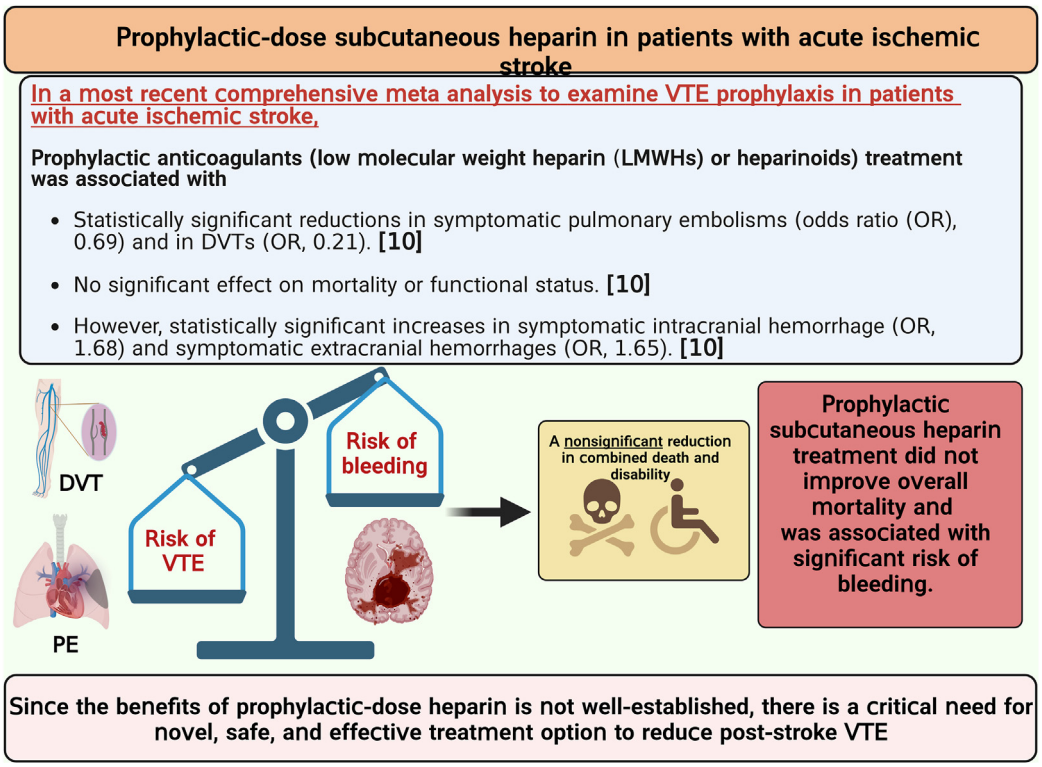
Essentials

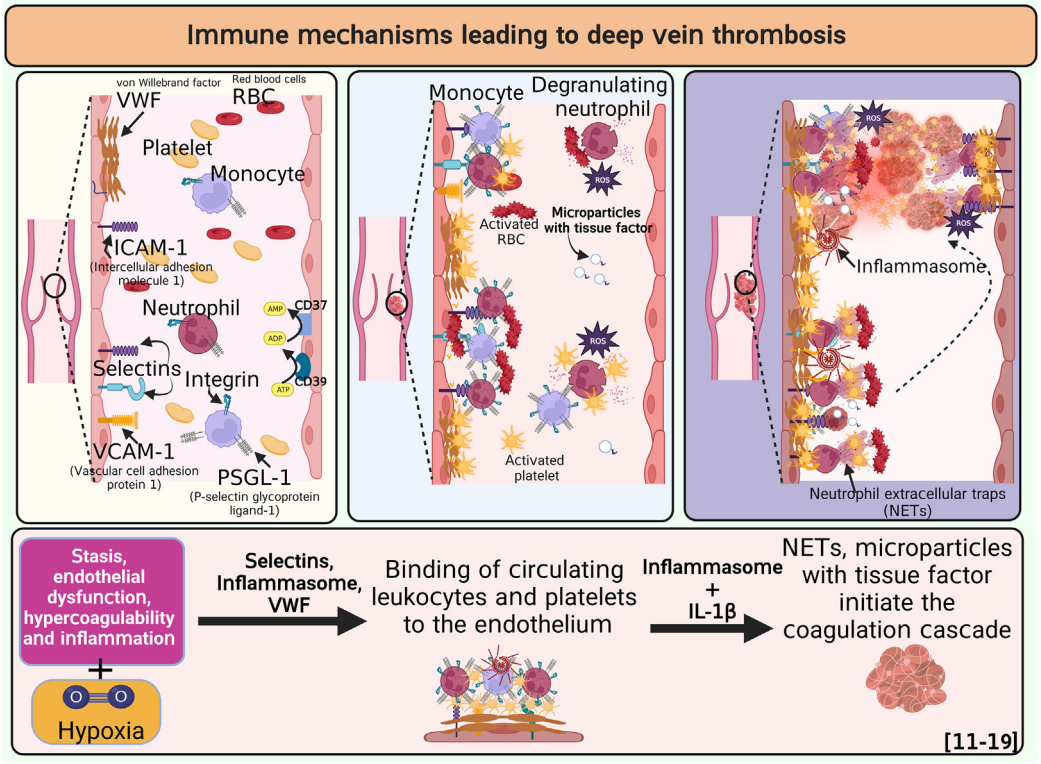
- Patients with acute ischemic stroke are at a high risk of venous thromboembolism (VTE).
- VTE is associated with increased risk of death and disability in patients with stroke.
- Interactions between neutrophils and other cells and factors contribute to risk of VTE.
- Current literature supports a key role of neutrophil-dependent mechanisms in promoting VTE.

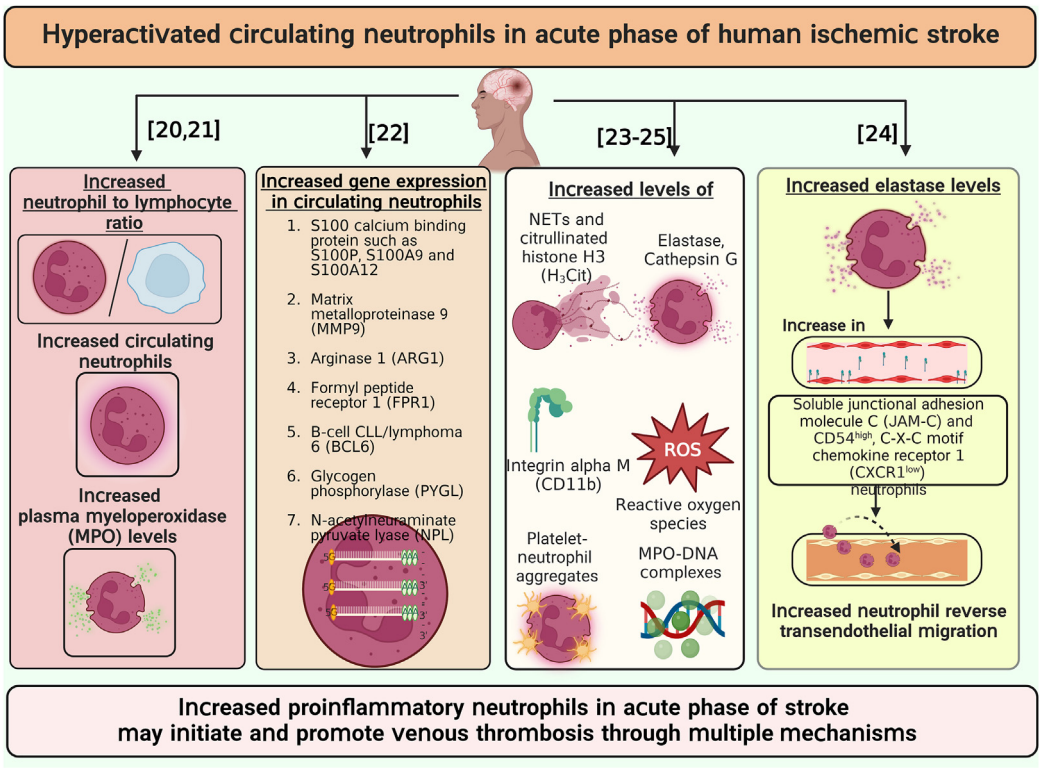


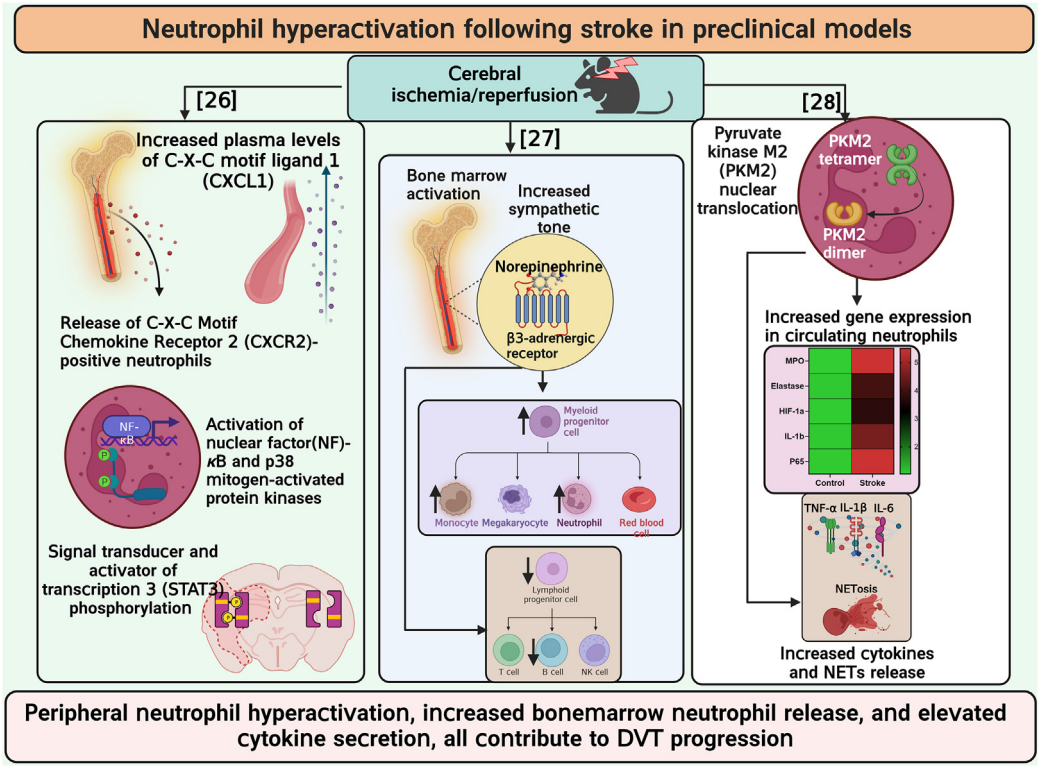


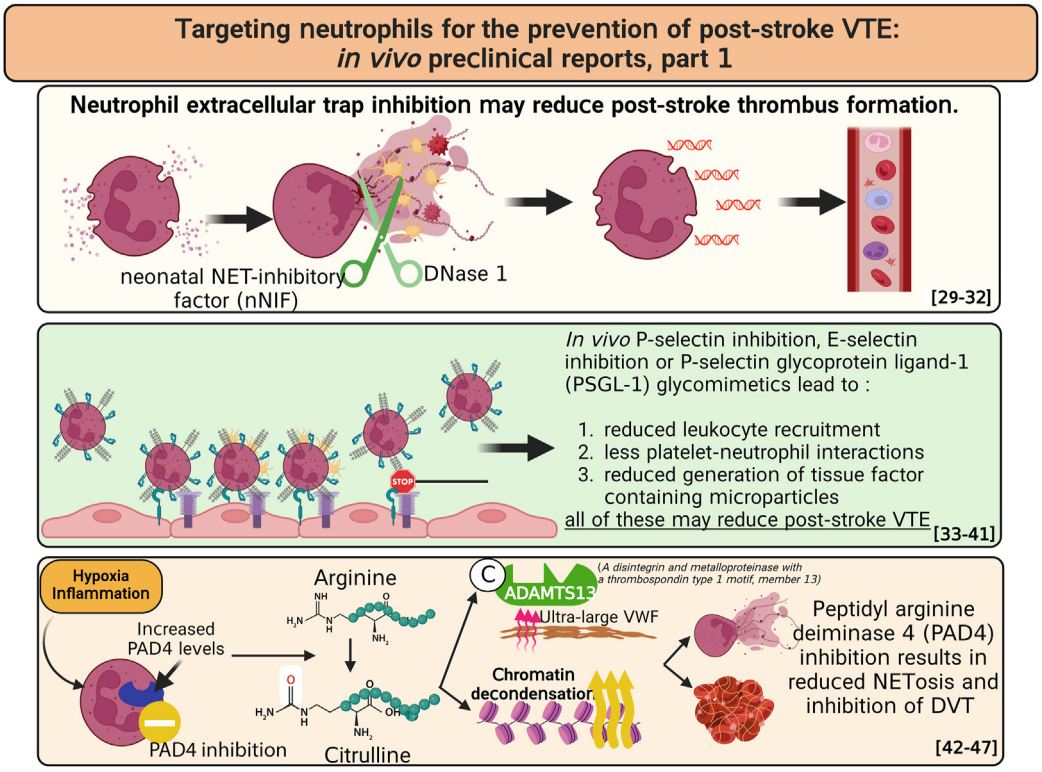

Prevention of post-stroke VTE: pharmacological approach
Anticoagulants : Low molecular weight heparin (Enoxaparin/Dalteparin/Danaparoid),
Unfractionated heparin (prophylactic dose)
Direct oral anticoagulants (Dabigatran/Rivaroxaban/Apixaban)
Antiplatelet agents: Aspirin/Clopidogrel
International Stroke Trial (IST) [8]
Clinical Trials
TOAST trial [9]
No aspirin N=9716
Aspirin N=9718
No heparin N=9719
Heparin N=9714
Placebo+best medical care N=638
Danaparoid+best medical care N=628
PE
Relative risk
Numbers needed to treat
Heparin 0.65 341
Aspirin 0.73 484
VTE
Relative risk
Numbers needed to treat
0.28 62
Hemorrhage
Relative risk
Numbers needed to harm
Heparin 3.4 105
Aspirin 1.9 187
Peripheral and brain bleeds
Relative risk
Numbers needed to harm
2.1 24
Antithrombotics reduce the risk of post-stroke VTE but increase bleeding risk

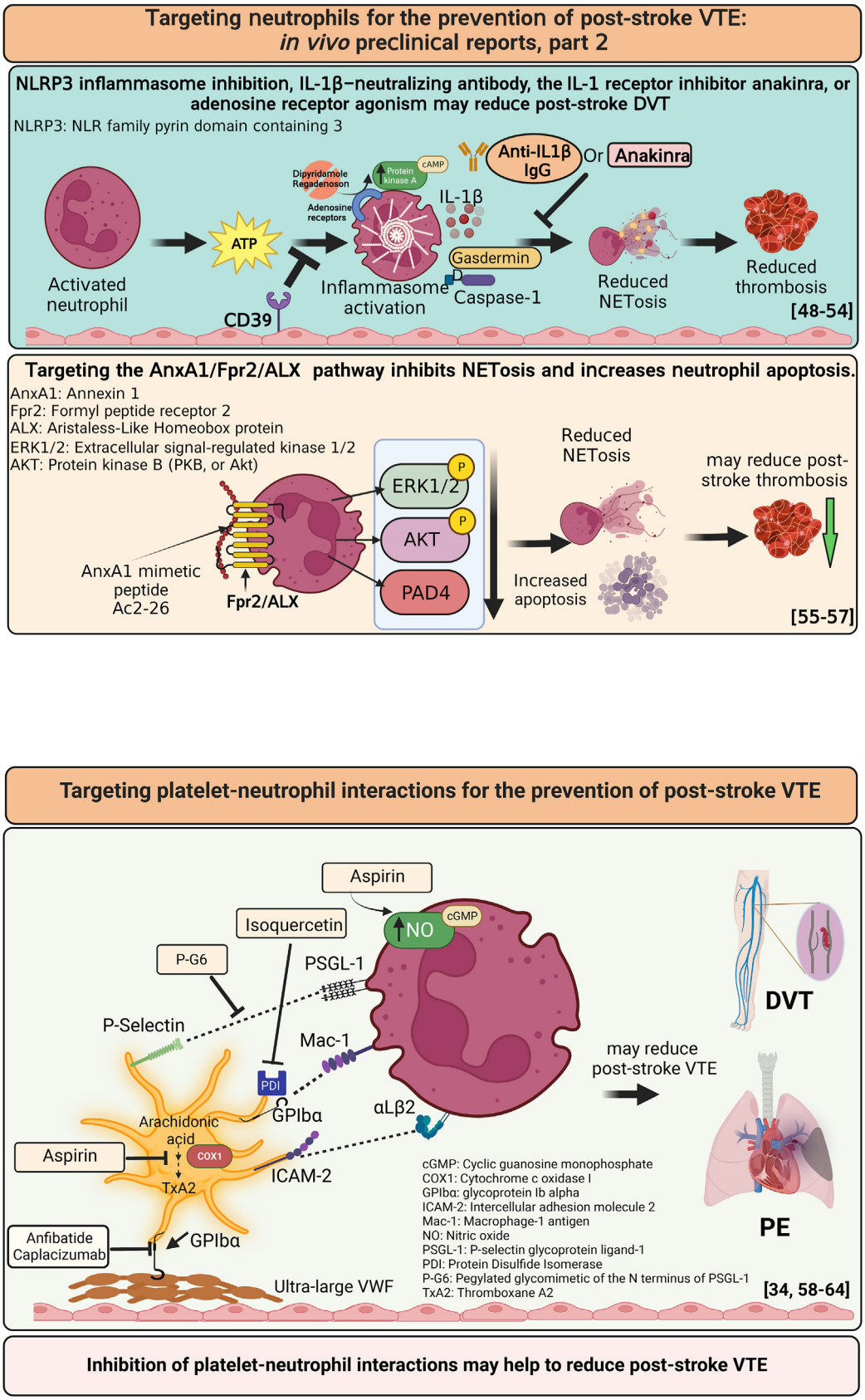

Prophylactic-dose subcutaneous heparin in patients with acute ischemic stroke
In a most recent comprehensive meta analysis to examine VTE prophylaxis in patients with acute ischemic stroke,
Prophylactic anticoagulants (low molecular weight heparin (LMWHs) or heparinoids) treatment was associated with
• Statistically significant reductions in symptomatic pulmonary embolisms (odds ratio (OR), 0.69) and in DVTs (OR, 0.21). [10]
• No significant effect on mortality or functional status. [10]
• However, statistically significant increases in symptomatic intracranial hemorrhage (OR, 1.68) and symptomatic extracranial hemorrhages (OR, 1.65). [10]
DVT
PE
Risk of VTE
Risk of bleeding
A nonsignificant reduction in combined death and disability
Prophylactic subcutaneous heparin treatment did not improve overall mortality and was associated with significant risk of bleeding.
Since the benefits of prophylactic-dose heparin is not well-established, there is a critical need for novel, safe, and effective treatment option to reduce post-stroke VTE

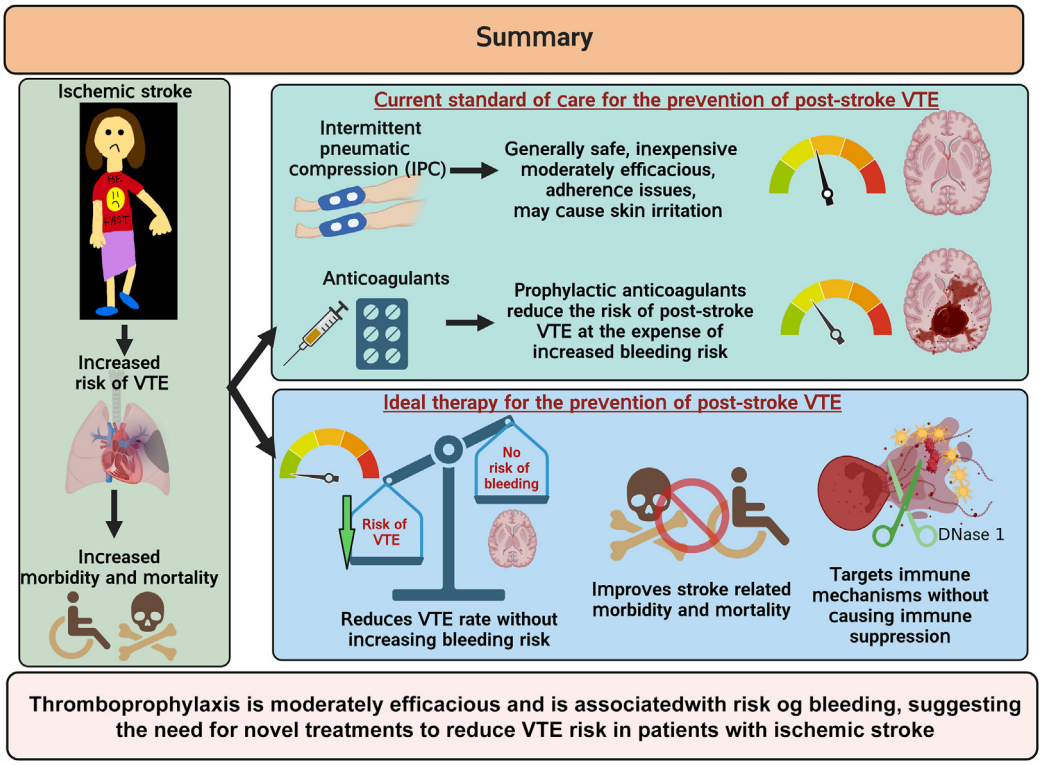

Immune mechanisms leading to deep vein thrombosis
von Willebrand factor
VWF
Red blood cells
RBC
Platelet
Monocyte
ICAM-1
(Intercellular adhesion molecule 1)
Neutrophil
CD37
CD39
Selectins
Integrin
VCAM-1
(Vascular cell adhesion protein 1)
PSGL-1
(P-selectin glycoprotein ligand-1)
Monocyte
Degranulating neutrophil
Activated RBC
Microparticles with tissue factor
Activated platelet
Inflammasome
Neutrophil extracellular traps (NETs)
Stasis, endothelial dysfunction, hypercoagulability and inflammation
Hypoxia
Selectins, Inflammasome, VWF
Binding of circulating leukocytes and platelets to the endothelium
Inflammasome + IL-1β
NETs, microparticles with tissue factor initiate the coagulation cascade
[11-19]


Hyperactivated circulating neutrophils in acute phase of human ischemic stroke
[20,21]
[22]
[23-25]
[24]
Increased neutrophil to lymphocyte ratio
Increased circulating neutrophils
Increased plasma myeloperoxidase (MPO) levels
Increased gene expression in circulating neutrophils
1. S100 calcium binding protein such as S100P, S100A9 and S100A12
2. Matrix metalloproteinase 9 (MMP9)
3. Arginase 1 (ARG1)
4. Formyl peptide receptor 1 (FPR1)
5. B-cell CLL/lymphoma 6 (BCL6)
6. Glycogen phosphorylase (PYGL)
7. N-acetylneuraminate pyruvate lyase (NPL)
Increased levels of
NETs and citrullinated histone H3 (H_3Cit)
Elastase, Cathepsin G
Integrin alpha M (CD11b)
ROS
Reactive oxygen species
Platelet-neutrophil aggregates
MPO-DNA complexes
Increased elastase levels
Increase in
Soluble junctional adhesion molecule C (JAM-C) and $CD54^{high}$, C-X-C motif chemokine receptor 1 ($CXCR1^{low}$) neutrophils
Increased neutrophil reverse transendothelial migration
Increased proinflammatory neutrophils in acute phase of stroke may initiate and promote venous thrombosis through multiple mechanisms


Neutrophil hyperactivation following stroke in preclinical models
Cerebral ischemia/reperfusion
[26]
[27]
[28]
Increased plasma levels of C-X-C motif ligand 1 (CXCL1)
Release of C-X-C Motif Chemokine Receptor 2 (CXCR2)-positive neutrophils
Activation of nuclear factor(NF)-κB and p38 mitogen-activated protein kinases
Signal transducer and activator of transcription 3 (STAT3) phosphorylation
Bone marrow activation
Increased sympathetic tone
Norepinephrine
β3-adrenergic receptor
Myeloid progenitor cell
Monocyte
Megakaryocyte
Neutrophil
Red blood cell
Lymphoid progenitor cell
T cell
B cell
NK cell
Pyruvate kinase M2 (PKM2) nuclear translocation
PKM2 tetramer
PKM2 dimer
Increased gene expression in circulating neutrophils
MPO
Elastase
HIF-1a
IL-1b
P65
Control
Stroke
TNF-α IL-1β IL-6
NETosis
Increased cytokines and NETs release
Peripheral neutrophil hyperactivation, increased bonemarrow neutrophil release, and elevated cytokine secretion, all contribute to DVT progression


Targeting neutrophils for the prevention of post-stroke VTE: *in vivo* preclinical reports, part 1
Neutrophil extracellular trap inhibition may reduce post-stroke thrombus formation.
neonatal NET-inhibitory factor (nNIF)
DNase 1
[29-32]
In vivo P-selectin inhibition, E-selectin inhibition or P-selectin glycoprotein ligand-1 (PSGL-1) glycomimetics lead to :
1. reduced leukocyte recruitment
2. less platelet-neutrophil interactions
3. reduced generation of tissue factor containing microparticles
all of these may reduce post-stroke VTE
STOP
[33-41]
Hypoxia Inflammation
Increased PAD4 levels
PAD4 inhibition
Arginine
Citrulline
ADAMTS13
(A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13)
Ultra-large VWF
Chromatin decondensation
Peptidyl arginine deiminase 4 (PAD4) inhibition results in reduced NETosis and inhibition of DVT
[42-47]


Targeting neutrophils for the prevention of post-stroke VTE:
in vivo preclinical reports, part 2
NLRP3 inflammasome inhibition, IL-1β–neutralizing antibody, the IL-1 receptor inhibitor anakinra, or adenosine receptor agonism may reduce post-stroke DVT
NLRP3: NLR family pyrin domain containing 3
Activated neutrophil
ATP
CD39
Dipyridamole Regadenoson
Adenosine receptors
cAMP
Protein kinase A
Inflammasome activation
IL-1β
Anti-IL1β IgG
Or
Anakinra
Gasdermin
Caspase-1
Reduced NETosis
Reduced thrombosis
[48-54]
Targeting the AnxA1/Fpr2/ALX pathway inhibits NETosis and increases neutrophil apoptosis.
AnxA1: Annexin 1
Fpr2: Formyl peptide receptor 2
ALX: Aristaless-Like Homeobox protein
ERK1/2: Extracellular signal-regulated kinase 1/2
AKT: Protein kinase B (PKB, or Akt)
AnxA1 mimetic peptide Ac2-26
Fpr2/ALX
ERK1/2
AKT
PAD4
P
Reduced NETosis
Increased apoptosis
may reduce post-stroke thrombosis
[55-57]
Targeting platelet-neutrophil interactions for the prevention of post-stroke VTE
Aspirin
Isoquercetin
P-G6
PSGL-1
P-Selectin
Mac-1
NO
cGMP
PDI
GPIbα
αLβ2
Arachidonic acid
COX1
TxA2
ICAM-2
Anfibatide Caplacizumab
Ultra-large VWF
may reduce post-stroke VTE
DVT
PE
cGMP: Cyclic guanosine monophosphate
COX1: Cytochrome c oxidase I
GPIbα: glycoprotein Ib alpha
ICAM-2: Intercellular adhesion molecule 2
Mac-1: Macrophage-1 antigen
NO: Nitric oxide
PSGL-1: P-selectin glycoprotein ligand-1
PDI: Protein Disulfide Isomerase
P-G6: Pegylated glycomimetic of the N terminus of PSGL-1
TxA2: Thromboxane A2
[34, 58-64]
Inhibition of platelet-neutrophil interactions may help to reduce post-stroke VTE



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AUTHOR CONTRIBUTIONS

N.D. developed the concepts, wrote the manuscript, and produced the illustrations. N.P., H.K., and C.V. edited the manuscript. J.A. and K.Y.S. cowrote the manuscript and edited the illustrations.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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REFERENCES

[1] Kelly J, Rudd A, Lewis R, Hunt BJ. Venous thromboembolism after acute stroke. *Stroke*. 2001;32:262–7.
[2] Kelly J, Rudd A, Lewis RR, Coshall C, Moody A, Hunt BJ. Venous thromboembolism after acute ischemic stroke: a prospective study using magnetic resonance direct thrombus imaging. *Stroke*. 2004;35:2320–5.
[3] Rinde LB, Småbrekke B, Mathiesen EB, Løchen ML, Njølstad I, Hald EM, et al. Ischemic stroke and risk of venous thromboembolism in the general population: the Tromsø study. *J Am Heart Assoc*. 2016;5:e004311.
[4] Garg A, Dhanesha N, Shaban A, Samaniego EA, Chauhan AK, Leira EC. Risk of venous thromboembolism in hospitalized patients with acute ischemic stroke versus other neurological conditions. *J Stroke Cerebrovasc Dis*. 2021;30:106077.
[5] Pongmoragot J, Rabinstein AA, Nilanont Y, Swartz RH, Zhou L, Saposnik G, et al. Pulmonary embolism in ischemic stroke: clinical presentation, risk factors, and outcome. *J Am Heart Assoc*. 2013;2:e000372.
[6] CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration, Dennis M, Sandercock P, Reid J, Graham C, Forbes J, et al. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. *Lancet*. 2013;382:516–24.
[7] Zhang D, Li F, Li X, Du G. Effect of intermittent pneumatic compression on preventing deep vein thrombosis among stroke patients: a systematic review and meta-analysis. *Worldviews Evid Based Nurs*. 2018;15:189–96.

[8] The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. *Lancet*. 1997;349:1569–81.

[9] Low molecular weight heparinoid, ORG 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. *JAMA*. 1998;279:1265–72.

[10] Dennis M, Caso V, Kappelle LJ, Pavlovic A, Sandercock P. European Stroke Organisation. European Stroke Organization (ESO) guidelines for prophylaxis for venous thromboembolism in immobile patients with acute ischaemic stroke. *Eur Stroke J*. 2016;1:6–19.

[11] Khan F, Tritschler T, Kahn SR, Rodger MA. Venous thromboembolism. *Lancet*. 2021;398:64–77.

[12] Budnik I, Brill A. Immune factors in deep vein thrombosis initiation. *Trends Immunol*. 2018;39:610–23.

[13] Kapoor S, Opneja A, Nayak L. The role of neutrophils in thrombosis. *Thromb Res*. 2018;170:87–96.

[14] Dhanesha N, Jain M, Doddapattar P, Undas A, Chauhan AK. Cellular fibronectin promotes deep vein thrombosis in diet-induced obese mice. *J Thromb Haemost*. 2021;19:814–21.

[15] Fuchs TA, Brill A, Wagner DD. Neutrophil extracellular trap (NET) impact on deep vein thrombosis. *Arterioscler Thromb Vasc Biol*. 2012;32:1777–83.

[16] Lester PA, Diaz JA, Shuster KA, Henke PK, Wakefield TW, Myers DD. Inflammation and thrombosis: new insights. *Front Biosci (Schol Ed)*. 2012;4:620–38.

[17] Kimball AS, Obi AT, Diaz JA, Henke PK. The emerging role of NETs in venous thrombosis and immunothrombosis. *Front Immunol*. 2016;7:236.

[18] Wolberg AS, Rosendaal FR, Weitz JI, Jaffer IH, Agnelli G, Baglin T, et al. Venous thrombosis. *Nat Rev Dis Primers*. 2015;1:15006.

[19] Byrnes JR, Wolberg AS. Red blood cells in thrombosis. *Blood*. 2017;130:1795–9.

[20] Maestrini I, Strbian D, Gautier S, Haapaniemi E, Moulin S, Sairanen T, et al. Higher neutrophil counts before thrombolysis for cerebral ischemia predict worse outcomes. *Neurology*. 2015;85:1408–16.

[21] Xue J, Huang W, Chen X, Li Q, Cai Z, Yu T, et al. Neutrophil-to-lymphocyte ratio is a prognostic marker in acute ischemic stroke. *J Stroke Cerebrovasc Dis*. 2017;26:650–7.

[22] Maestrini I, Tagzirt M, Gautier S, Dupont A, Mendyk AM, Susen S, et al. Analysis of the association of MPO and MMP-9 with stroke severity and outcome: cohort study. *Neurology*. 2020;95:e97–108.

[23] Tang Y, Xu H, Du X, Lit L, Walker W, Lu A, et al. Gene expression in blood changes rapidly in neutrophils and monocytes after ischemic stroke in humans: a microarray study. *J Cereb Blood Flow Metab*. 2006;26:1089–102.

[24] Weisenburger-Lile D, Dong Y, Yger M, Weisenburger G, Polara GF, Chaigneau T, et al. Harmful neutrophil subsets in patients with ischemic stroke: association with disease severity. *Neurol Neuroimmunol Neuroinflamm*. 2019;6:e571.

[25] Denorme F, Portier I, Rustad JL, Cody MJ, de Araujo CV, Hoki C, et al. Neutrophil extracellular traps regulate ischemic stroke brain injury. *J Clin Invest*. 2022;132:e154225.

[26] Denes A, McColl BW, Leow-Dyke SF, Chapman KZ, Humphreys NE, Grencis RK, et al. Experimental stroke-induced changes in the bone marrow reveal complex regulation of leukocyte responses. *J Cereb Blood Flow Metab*. 2011;31:1036–50.

[27] Courties G, Herisson F, Sager HB, Heidt T, Ye Y, Wei Y, et al. Ischemic stroke activates hematopoietic bone marrow stem cells. *Circ Res*. 2015;116:407–17.

[28] Dhanesha N, Patel RB, Doddapattar P, Ghatge M, Flora GD, Jain M, et al. PKM2 promotes neutrophil activation and cerebral thromboinflammation: therapeutic implications for ischemic stroke. *Blood*. 2022;139:1234–45.

[29] Fuchs TA, Brill A, Duerschmied D, Schatzberg D, Monestier M, Myers Jr DD, et al. Extracellular DNA traps promote thrombosis. *Proc Natl Acad Sci U S A*. 2010;107:15880–5.

[30] von Brühl ML, Stark K, Steinhart A, Chandraratne S, Konrad I, Lorenz M, et al. Monocytes, neutrophils, and platelets cooperate to initiate and propagate venous thrombosis in mice in vivo. *J Exp Med*. 2012;209:819–35.

[31] Kumar R, Sonkar VK, Swamy J, Ahmed A, Sharathkumar AA, Pierce GL, et al. DNase 1 protects from increased thrombin generation and venous thrombosis during aging: cross-sectional study in mice and humans. *J Am Heart Assoc*. 2022;11:e021188.

[32] Brill A, Fuchs TA, Savchenko AS, Thomas GM, Martinod K, De Meyer SF, et al. Neutrophil extracellular traps promote deep vein thrombosis in mice. *J Thromb Haemost*. 2012;10:136–44.

[33] Diaz JA, Wrobleski SK, Alvarado CM, Hawley AE, Doornbos NK, Lester PA, et al. P-selectin inhibition therapeutically promotes thrombus resolution and prevents vein wall fibrosis better than enoxaparin and an inhibitor to von Willebrand factor. *Arterioscler Thromb Vasc Biol*. 2015;35:829–37.

[34] Wong DJ, Park DD, Park SS, Haller CA, Chen J, Dai E, et al. A PSGL-1 glycomimetic reduces thrombus burden without affecting hemostasis. *Blood*. 2021;138:1182–93.

[35] Myers DD Jr, Wrobleski SK, Longo C, Bedard PW, Kaila N, Shaw GD, et al. Resolution of venous thrombosis using a novel oral small-molecule inhibitor of P-selectin (PSI-697) without anticoagulation. *Thromb Haemost*. 2007;97:400–7.

[36] Meier TR, Myers Jr DD, Wrobleski SK, Zajkowski PJ, Hawley AE, Bedard PW, et al. Prophylactic P-selectin inhibition with PSI-421 promotes resolution of venous thrombosis without anticoagulation. *Thromb Haemost*. 2008;99:343–51.

[37] Wakefield TW, Strieter RM, Downing LJ, Kadell AM, Wilke CA, Burdick MD, et al. P-selectin and TNF inhibition reduce venous thrombosis inflammation. *J Surg Res*. 1996;64:26–31.

[38] Downing LJ, Wakefield TW, Strieter RM, Prince MR, Londy FJ, Fowlkes JB, et al. Anti-P-selectin antibody decreases inflammation and thrombus formation in venous thrombosis. *J Vasc Surg*. 1997;25:816–27.

[39] Myers DD Jr, Rectenwald JE, Bedard PW, Kaila N, Shaw GD, Schaub RG, et al. Decreased venous thrombosis with an oral inhibitor of P selectin. *J Vasc Surg*. 2005;42:329–36.

[40] Myers DD Jr, Ning J, Lester P, Adili R, Hawley A, Durham L, et al. E-selectin inhibitor is superior to low-molecular-weight heparin for the treatment of experimental venous thrombosis. *J Vasc Surg Venous Lymphat Disord*. 2022;10:211–20.

[41] Culmer DL, Dunbar ML, Hawley AE, Sood S, Sigler RE, Henke PK, et al. E-selectin inhibition with GMI-1271 decreases venous thrombosis without profoundly affecting tail vein bleeding in a mouse model. *Thromb Haemost*. 2017;117:1171–81.

[42] Sundd P, Pospieszalska MK, Ley K. Neutrophil rolling at high shear: flattening, catch bond behavior, tethers and slings. *Mol Immunol*. 2013;55:59–69.

[43] Ley K, Hoffman HM, Kubes P, Cassatella MA, Zychlinsky A, Hedrick CC, et al. Neutrophils: new insights and open questions. *Sci Immunol*. 2018;3:4579.

[44] Sorvillo N, Mizurini DM, Coxon C, Martinod K, Tilvawala R, Cherpokova D, et al. Plasma peptidylarginine deiminase IV promotes VWF-platelet string formation and accelerates thrombosis after vessel injury. *Circ Res*. 2019;125:507–19.

[45] Lewis HD, Liddle J, Coote JE, Atkinson SJ, Barker MD, Bax BD, et al. Inhibition of PAD4 activity is sufficient to disrupt mouse and human NET formation. *Nat Chem Biol*. 2015;11:189–91.

[46] Martinod K, Demers M, Fuchs TA, Wong SL, Brill A, Gallant M, et al. Neutrophil histone modification by peptidylarginine deiminase 4 is critical for deep vein thrombosis in mice. *Proc Natl Acad Sci U S A*. 2013;110:8674–9.

[47] Ansari J, Vital SA, Yadav S, Gavins FNE. Regulating neutrophil PAD4/NOX-dependent cerebrovasular thromboinflammation. *Int J Biol Sci*. 2023;19:852–64.

[48] Colling ME, Tourdot BE, Kanthi Y. Inflammation, infection and venous thromboembolism. *Circ Res*. 2021;128:2017–36.

[49] Kanthi YM, Sutton NR, Pinsky DJ. CD39: interface between vascular thrombosis and inflammation. *Curr Atheroscler Rep*. 2014;16:425.

[50] Yadav V, Chi L, Zhao R, Tourdot BE, Yalavarthi S, Jacobs BN, et al. Ectonucleotidase tri(di)phosphohydrolase-1 (ENTPD-1) disrupts inflammasome/interleukin 1β-driven venous thrombosis. *J Clin Invest*. 2019;129:2872–7.

[51] Anyanwu AC, Kanthi Y, Fukase K, Liao H, Mimura T, Desch KC, et al. Tuning the thromboinflammatory response to venous flow interruption by the ectonucleotidase CD39. *Arterioscler Thromb Vasc Biol*. 2019;39:e118–29.

[52] Zhang Y, Cui J, Zhang G, Wu C, Abdel-Latif A, Smyth SS, et al. Inflammasome activation promotes venous thrombosis through pyroptosis. *Blood Adv*. 2021;5:2619–23.

[53] Gupta N, Sahu A, Prabhakar A, Chatterjee T, Tyagi T, Kumari B, et al. Activation of NLRP3 inflammasome complex potentiates venous thrombosis in response to hypoxia. *Proc Natl Acad Sci U S A*. 2017;114:4763–8.

[54] Ali RA, Gandhi AA, Meng H, Yalavarthi S, Vreede AP, Estes SK, et al. Adenosine receptor agonism protects against NETosis and thrombosis in antiphospholipid syndrome. *Nat Commun*. 2019;10:1916.

[55] Ansari J, Senchenkova EY, Vital SA, Al-Yafeai Z, Kaur G, Sparkenbaugh EM, et al. Targeting the AnxA1/Fpr2/ALX pathway regulates neutrophil function, promoting thromboinflammation resolution in sickle cell disease. *Blood*. 2021;137:1538–49.

[56] Sanches JM, Correia-Silva RD, Duarte GHB, Fernandes AMAP, Sánchez-Vinces S, Carvalho PO, et al. Role of annexin A1 in NLRP3 inflammasome activation in murine neutrophils. *Cells*. 2021;10:121.

[57] Vago JP, Nogueira CR, Tavares LP, Soriani FM, Lopes F, Russo RC, et al. Annexin A1 modulates natural and glucocorticoid-induced resolution of inflammation by enhancing neutrophil apoptosis. *J Leukoc Biol*. 2012;92:249–58.

[58] López-Farré A, Caramelo C, Esteban A, Alberola ML, Millás I, Montón M, et al. Effects of aspirin on platelet-neutrophil interactions. Role of nitric oxide and endothelin-1. *Circulation*. 1995;91:2080–8.

[59] Zwicker JI, Schlechter BL, Stopa JD, Liebman HA, Aggarwal A, Puligandla M, et al. Targeting protein disulfide isomerase with the flavonoid isoquercetin to improve hypercoagulability in advanced cancer. *JCI Insight*. 2019;4:e125851.

[60] Li J, Kim K, Jeong SY, Chiu J, Xiong B, Petukhov PA, et al. Platelet protein disulfide isomerase promotes glycoprotein Ibα-mediated platelet-neutrophil interactions under thromboinflammatory conditions. *Circulation*. 2019;139:1300–19.

[61] Li BX, Dai X, Xu XR, Adili R, Neves MAD, Lei X, et al. In vitro assessment and phase I randomized clinical trial of anfibatide a snake venom derived anti-thrombotic agent targeting human platelet GPIbα. *Sci Rep*. 2021;11:11663.

[62] Xu XR, Carrim N, Neves MA, McKeown T, Stratton TW, Coelho RM, et al. Platelets and platelet adhesion molecules: novel mechanisms of thrombosis and anti-thrombotic therapies. *Thromb J*. 2016;14(Suppl 1):29.

[63] Scully M, Cataland SR, Peyvandi F, Coppo P, Knöbl P, Kremer Hovinga JA, et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. *N Engl J Med*. 2019;380:335–46.

[64] Li J, Kim K, Barazia A, Tseng A, Cho J. Platelet-neutrophil interactions under thromboinflammatory conditions. *Cell Mol Life Sci*. 2015;72:2627–43.