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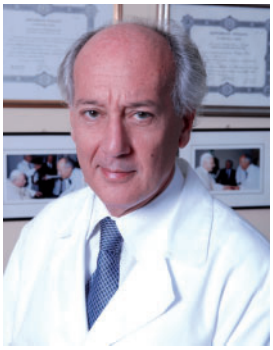
Thrombosis in peripheral artery disease and thrombotic thrombocytopenia after adenoviral COVID-19 vaccination



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This Focus Issue on thrombosis and antithrombotic treatment starts with the Special Article 'Antithrombotic therapies in aortic and peripheral arterial diseases in 2021: a consensus document from the ESC working group on aorta and peripheral vascular diseases, the ESC working group on thrombosis, and the ESC working group on cardiovascular pharmacotherapy' by Victor Aboyans from the University of Limoges in France, and colleagues.[1] The aim of this collaborative document is to provide an update for clinicians on best antithrombotic strategies in patients with aortic and/or peripheral arterial diseases. Antithrombotic therapy is a pillar of optimal medical treatment for these patients at very high cardiovascular risk (*Figure 1*).[1–3]

While the number of trials on antithrombotic therapies in patients with aortic or peripheral arterial diseases is substantially smaller than for those with coronary artery disease (CAD), recent evidence deserves to be incorporated into clinical practice. In the absence of specific indications for chronic oral anticoagulation due to concomitant cardiovascular disease, a single antiplatelet agent is the basis for long-term antithrombotic treatment in patients with aortic or peripheral arterial diseases. Its association with another antiplatelet agent or low-dose anticoagulants is also discussed, based on a patient's ischaemic and bleeding risk as well as therapeutic paths (e.g. endovascular therapy). This consensus document aims to provide guidance on antithrombotic therapy according to arterial disease localizations and clinical presentation. It cannot, however, substitute for multidisciplinary team discussions, which are particularly important for patients with an uncertain ischaemic/bleeding balance. Importantly, since this balance evolves over time in an individual patient, a regular reassessment of the antithrombotic therapy is of the utmost importance.

Opioids remain the analgesic agent of choice in managing myocardial ischaemic pain. However, retrospective studies have raised concerns regarding potential interactions between opioids and oral $P2Y_{12}$ inhibitors, which are a cornerstone of therapy in myocardial infarction.[4,5] In an ESC Fast Track article entitled '**Effects of lignocaine vs. opioids on antiplatelet activity of ticagrelor: the LOCAL trial**', Himawan Fernando from Monash University in Melbourne, Australia, and colleagues assessed the impact of intravenous fentanyl and lignocaine on the pharmacokinetics and pharmacodynamics of ticagrelor in patients with unstable angina and non-ST-segment elevation myocardial infarction and their procedural analgesic efficacy and safety.[6] Seventy patients undergoing coronary angiography with ticagrelor loading were included in the pharmacokinetic and pharmacodynamic analyses of this randomized trial. Plasma ticagrelor levels 2 hours post-loading dose were significantly lower in the fentanyl arm than in the lignocaine treatment arm (598 vs. 1008 ng/mL, $P = 0.014$). The area under the plasma–time curves for ticagrelor (1228 vs. 2753 ng h/mL, $P < 0.001$) and its active metabolite (201 vs. 447 ng h/mL, $P = 0.001$) were both significantly lower in the fentanyl arm. Expression of activated platelet glycoprotein IIb/IIIa receptor and P-selectin was significantly higher at 60 min in the fentanyl arm. A higher proportion of patients had high on-treatment platelet reactivity in the fentanyl arm.

The authors conclude that unlike fentanyl, lignocaine does not impair the bioavailability or delay the antiplatelet effect of ticagrelor. Both drugs were well tolerated and effective, with a high level of patient satisfaction for procedural analgesia. Routine procedural analgesia during percutaneous coronary intervention (PCI) should be

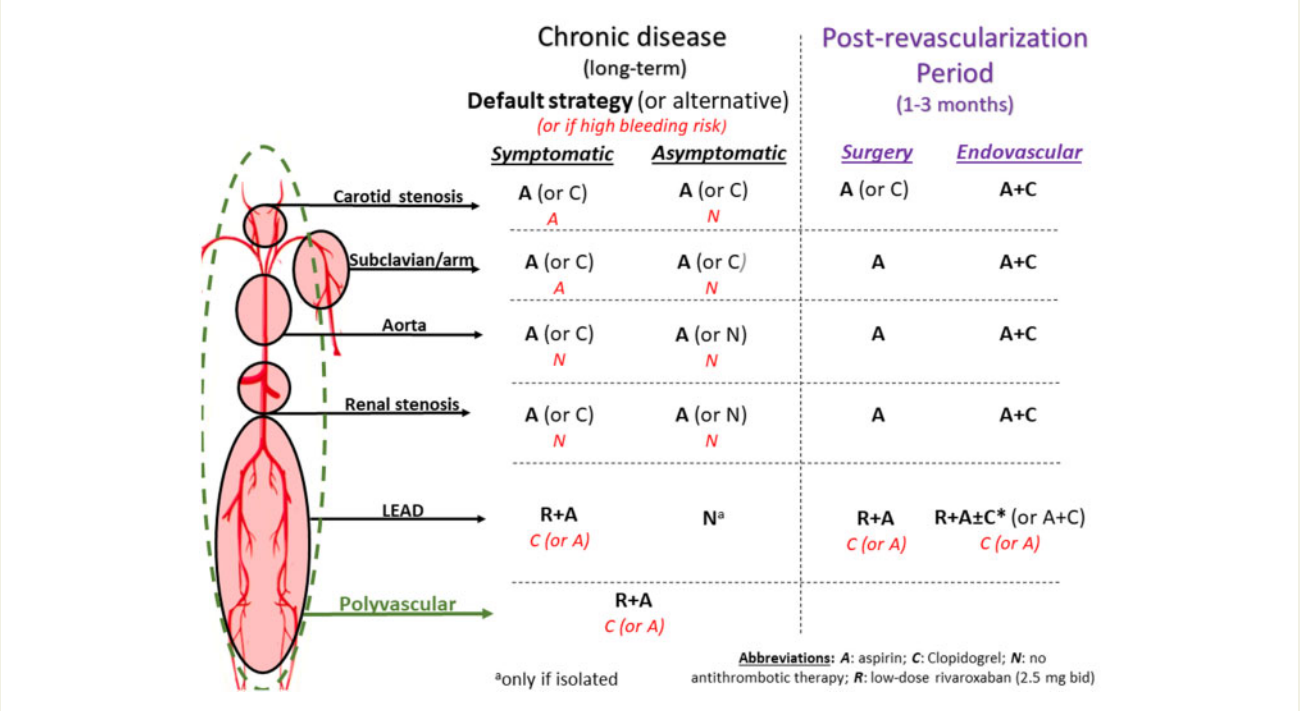

Figure 1 Graphical Abstract (from Aboyans V, Bauersachs R, Mazzolai L, Brodmann M, Palomares JFR, Debus S, Collet JP, Drexel H, Espinola-Klein C, Lewis BS, Roffi M, Sibbing D, Sillesen H, Stabile E, Schlager O, De Carlo M. Antithrombotic therapies in aortic and peripheral arterial diseases in 2021: a consensus document from the ESC working group on aorta and peripheral vascular diseases, the ESC working group on thrombosis, and the ESC working group on cardiovascular pharmacotherapy. See pages 4013–4024).

reconsidered and, if performed, lignocaine is a beneficial alternative to fentanyl. The manuscript is accompanied by an **Editorial** by Dominick Angiolillo and Mattia Galli from the University of Florida College of Medicine in Jacksonville, FL, USA.[7] The authors conclude that although the available evidence on the use of non-opioid analgesics in patients undergoing coronary angiography and PCI are thus far promising, whether they can be safely and effectively used as a mainstream treatment in this setting remains to be seen.

Peripheral artery disease (PAD) is a progressive atherosclerotic disorder; it can be asymptomatic, but often results in profound functional limitation, acute limb-threatening ischaemia, and amputation.[8–12] More than 235 million individuals worldwide are afflicted, and age is one of the most important risk factors for PAD. Despite an elevated risk for major adverse limb events and major adverse cardiovascular events, patients with PAD are less likely to be treated with antithrombotic therapy compared with their CAD counterparts, In another ESC Fast Track article entitled '**Low-dose rivaroxaban plus aspirin in older patients with peripheral artery disease undergoing acute limb revascularization: insights from the VOYAGER PAD trial**', Mori Krantz from the University of Colorado School of Medicine in Aurora, CO, USA, and colleagues indicate that in their secondary analysis of the VOYAGER trial, rivaroxaban 2.5 mg twice a day plus aspirin 100 mg a day vs aspirin only was assessed in older adults. Advanced age is associated with elevated bleeding risk and unfavourable net benefit for dual antiplatelet therapy in chronic CAD.[13] The risk–benefit of low-dose rivaroxaban in patients ≥75 years old with PAD after lower extremity revascularization (LER) has not been described. The primary endpoint was a composite of acute limb ischaemia, major amputation, myocardial infarction, ischaemic stroke, or cardiovascular death. The principal safety outcome was thrombolysis in myocardial infarction (TIMI) major bleeding analysed by the pre-specified age cut-off of 75 years. Of 6564 patients randomized, 1330 (20%) were >75 years. Absolute 3-year Kaplan–Meier cumulative incidence rates for primary efficacy (23% vs. 19%) and safety (3.5% vs. 1.5%) endpoints were higher in elderly vs. non-elderly patients. The efficacy (*P*-interaction 0.83) and safety (*P*-interaction 0.38) of rivaroxaban were consistent irrespective of age. The combination of intracranial and fatal bleeding was not increased in patients >75 years. Overall, benefits (absolute risk reduction 3.8%, number needed to treat 26 for the primary endpoint) exceeded risks (absolute risk increase 0.81%, number needed to harm 123 for TIMI major bleeding).

The authors conclude that patients ≥75 years old with PAD are at both heightened ischaemic and bleeding risk after LER. No excess harm with respect to major, intracranial, or fatal bleeding was seen in older patients, yet numerically greater absolute benefits were observed. This suggests that low-dose rivaroxaban combined with aspirin should be considered in PAD after LER regardless of age. The manuscript is accompanied by an **Editorial** by Greg Lip, S.R. Vallabhaneni, and Juqian Zhang from the Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital in the UK.[14] The authors conclude that one priority

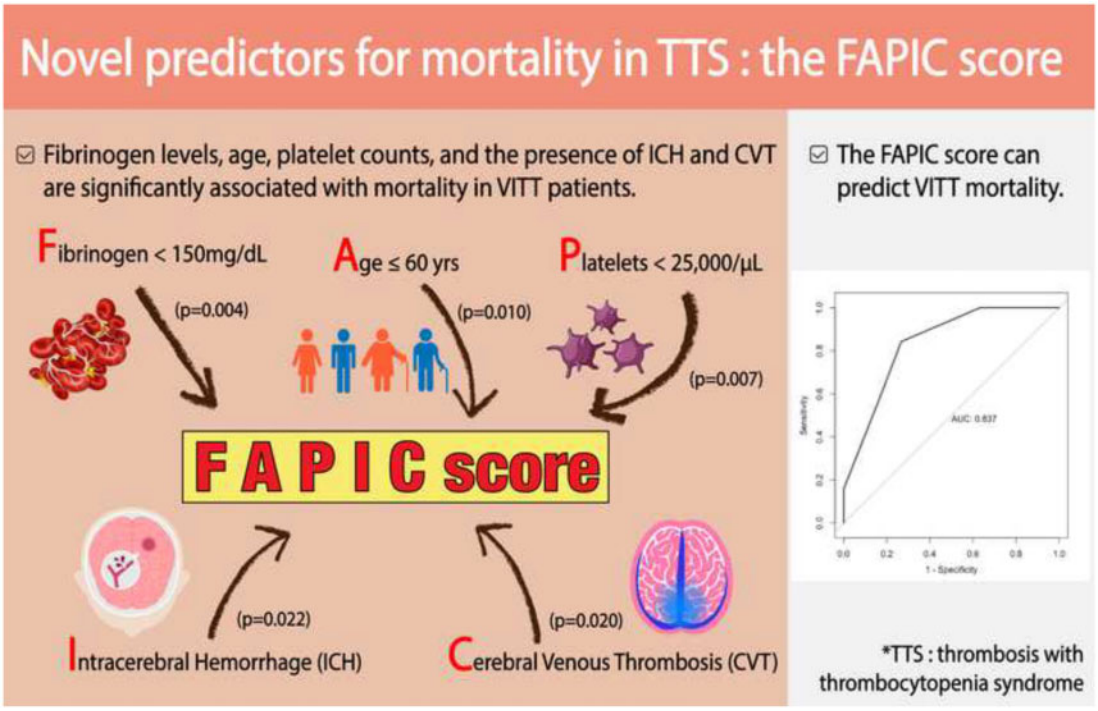

Figure 2 Graphical Abstract (from Hwang J, Park SH, Lee SW, Lee SB, Lee MH, Jeong GH, Kim MS, Kim JY, Koyanagi A, Jacob L, Jeong SY, Song JW, Yon DK, Shin JI, Smith L. Predictors of mortality in thrombotic thrombocytopenia after adenoviral COVID-19 vaccination: the FAPIC score. See pages 4053–4063).

is improving clinical risk stratification of PAD patients so rivaroxaban combined with aspirin could potentially benefit those with 'true' high risk but at an acceptable level of major but non-fatal bleeding.

In the past 18 months, we have published several studies on the cardiovascular implications of the coronavirus disease 2019 (COVID-19) pandemic.[15–17] The COVID-19 pandemic can only be overcome through a global effort leading to mass vaccination. Yet, only recently, Norway and Denmark stopped the ChAdOx1 nCoV-19 vaccination after several cases of vaccine-induced syndrome of severe thrombosis and thrombocytopenia with fatal outcome were reported. The clinical manifestation and outcomes of thrombosis with thrombocytopenia syndrome (TTS) after adenoviral COVID-19 vaccine administration are largely unknown due to the rare nature of the disease. In a Fast Track article entitled '**Predictors of mortality in thrombotic thrombocytopenia after adenoviral COVID-19 vaccination: the FAPIC score**', Jae Il Shin from the Yonsei University College of Medicine in Korea, and colleagues aimed to analyse the clinical presentation, treatment modalities, outcomes, and prognostic factors of adenoviral TTS, as well as identify predictors for mortality.[18] PubMed, Scopus, Embase, and Web of Science databases were searched, and the resulting articles were reviewed. A total of 6 case series and 13 case reports (64 patients) of TTS after ChAdOx1 nCoV-19 vaccination were included. The authors performed a pooled analysis and developed a novel scoring system to predict mortality. The overall mortality of TTS after ChAdOx1 nCoV-19 vaccination was 36%. In this study, age at or under 60, platelet count below $25 \times 10^3/\mu L$, fibrinogen below 150 mg/dL, the presence of intracerebral haemorrhage (ICH), and the presence of cerebral venous thrombosis (CVT) were significantly associated with death and were selected as predictors for mortality (1 point each). Shin *et al.* named this novel scoring system FAPIC (fibrinogen, age, platelet count, ICH, and CVT), and the C-statistic for the FAPIC score was 0.837. Expected mortality increased with each point increase in the FAPIC score, ranging from 2.08% to 90.05% (*Figure 2*). The FAPIC scoring model was internally validated through cross-validation and bootstrapping, then externally validated on a panel of TTS patients after Ad26.COV2.S administration. The authors conclude that fibrinogen levels, age, platelet counts, and the presence of ICH and CVT are significantly associated with mortality in patients with TTS, and the FAPIC score constituting these risk factors could predict mortality.

In a Fast Track manuscript entitled '**Immune complexes, innate immunity, and NETosis in ChAdOx1 vaccine-induced thrombocytopenia**', Sverre Holm from the Oslo University Hospital in Norway, and colleagues reported five cases of vaccine-induced immune thrombotic thrombocytopenia (VITT) 7–10 days after receiving the first dose of the ChAdOx1 nCoV-19 adenoviral vector vaccine against COVID-19.[19] They aimed to investigate the pathogenic immunological responses operating in these patients. The authors assessed circulating inflammatory markers by immune assays and immune cell phenotyping by flow cytometry analyses, and performed immunoprecipitation with antiplatelet factor 4 (PF4) antibody in plasma samples from all five patients followed by mass spectrometry. A thrombus was retrieved from the sinus sagittal superior of

one patient and analysed by immunohistochemistry and flow cytometry. Precipitated immune complexes revealed multiple innate immune pathway triggers for platelet and leucocyte activation. Plasma contained increased levels of innate immune response cytokines and markers of systemic inflammation, extensive degranulation of neutrophils, and tissue and endothelial damage. Blood analyses showed activation of neutrophils and increased levels of circulating H3Cit, double-stranded DNA, and myeloperoxidase–DNA complex. The thrombus had extensive infiltration of neutrophils, formation of neutrophil extracellular traps (NETs), and IgG deposits. The authors conclude that their results show that anti-PF4/polyanion IgG-mediated thrombus formation in VITT patients is accompanied by a massive innate immune activation and particularly by the fulminant activation of neutrophils including NETosis. These results provide novel data on the immune response in this rare adenoviral vector-induced VITT.

The two manuscripts by Shin *et al.* and Holm *et al.* are accompanied by a double **Editorial** by Jean Connors from the Harvard Medical School in Boston, MA, USA.[20] Connors concludes that what is clear is that VITT is a rare occurrence that we can now diagnose with identifiable clinical and laboratory features and can be treated appropriately, resulting in lower mortality. Although use of the adenoviral vector vaccines was put on temporary hold in some countries, use by most has understandably resumed given the >4 million deaths that have resulted from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Continued investigation to unravel the aetiological triggers of VITT using clinical and laboratory findings is warranted, not only to understand the pathophysiology of VITT and improve treatment, but also to identify critical knowledge that can be used in the future—with 3.9 billion doses of vaccine administered around the world to date, there is hope that this pandemic will soon be over.

Mental stress substantially contributes to the initiation and progression of human disease, including cardiovascular conditions. In a Translational Research article entitled '**Acute mental stress drives vascular inflammation and promotes plaque destabilization in mouse atherosclerosis**', Julia Hinterdobler from the Technical University Munich in Germany, and colleagues aimed to investigate the underlying mechanisms of these contributions since they remain largely unclear.[21] Here, they show in humans and mice that leucocytes deplete rapidly from the blood after a single episode of acute mental stress. Using cell-tracking experiments in animal models of acute mental stress, the authors found that stress exposure leads to prompt uptake of inflammatory leucocytes from the blood to distinct tissues including the heart, lung, skin, and, if present, atherosclerotic plaques. Mechanistically, they found that acute stress enhances leucocyte influx into mouse atherosclerotic plaques by modulating endothelial cells. Specifically, acute stress increases adhesion molecule expression and chemokine release through locally derived norepinephrine. Both chemical and surgical disruption of norepinephrine signalling diminished stress-induced leucocyte migration into mouse atherosclerotic plaques.

The authors conclude that their data show that acute mental stress rapidly amplifies inflammatory leucocyte expansion inside mouse atherosclerotic lesions and promotes plaque vulnerability. The contribution is accompanied by an **Editorial** by Amir Lerman from the Mayo Clinic in Rochester, MN, USA, and colleagues.[22] Lerman and colleagues point out that the study by Hinterdobler *et al.* helps to identify several key challenges and next steps in our attempt to learn more about this intriguing and relevant area, by shedding light on the central role of the endothelium as the effector cells of the neuroimmune response to mental stress.

The issue is also complemented by a Discussion Forum contribution. In a commentary entitled '**The neutrophil–lymphocyte ratio and incident atherosclerotic events: the impact of racial differences?**', Philippe Giral from the Sorbonne Université UMRS 1166 in France and colleagues comment on the recent publication '**The neutrophil–lymphocyte ratio and incident atherosclerotic events: analyses from five contemporary randomized trials'** by Nicholas H. Adamstein from Harvard Medical School in Boston, MA, USA.[23,24]

The editors hope that this issue of the *European Heart Journal* will be of interest to its readers.

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