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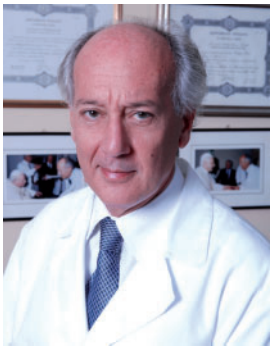
Pulmonary embolism, COVID, and bleeding risk in acute coronary syndromes: a Focus Issue on thrombosis and antithrombotic treatment



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This Issue opens with a joint Special Article entitled '**Clinician well-being—addressing global needs for improvements in the health care field: a joint opinion from the American College of Cardiology, American Heart Association, European Society of Cardiology, World Heart Federation**' by Laxmi Mehta from the Ohio State University Wexner Medical Center in the USA.[1] The authors note that as clinicians, we strive for improved health for our patients; yet, it is increasingly clear that our own well-being is an essential component of the quadruple aim: to improve population health, enhance patient experience, reduce costs, and improve the work life of healthcare workers. Clinician well-being is described as experiencing satisfaction and engagement with work, while also having a feeling of professional fulfilment and a sense of meaning in work. Conversely, burnout is an occupational phenomenon that is defined as emotional exhaustion, depersonalization, and a sense of low personal accomplishment in a perceived stressful work environment. Although burnout is a sign of clinical distress and a barrier to clinician well-being, its absence alone does not confer a state of well-being. Rather, burnout is one of the more extreme negative components along the spectrum of clinician well-being and can co-exist with other common mental conditions (e.g. anxiety and depression).

The Issue continues with a focus on thrombosis and antithrombotic treatment. Infection by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is mainly characterized by fever and respiratory symptoms, with dyspnoea and lung infiltrates in more severe cases. Many patients also present a procoagulant state. In this context, patients with coronavirus disease 2019 (COVID-19) have an increased risk of developing clinically thrombotic complications such as pulmonary embolism (PE). Immunological and inflammatory-related phenomena may play a role in PE development.[2–5] In a Clinical Research article entitled '**Pulmonary embolism in patients with COVID-19: incidence, risk factors, clinical characteristics, and outcome**', Òscar Miró from the University of Barcelona in Spain, and colleagues investigated the incidence, risk factors, clinical characteristics, and outcomes of PE in patients with COVID-19 attending emergency departments (EDs), before hospitalization.[6] The authors retrospectively reviewed all COVID patients diagnosed with PE in 62 Spanish EDs (20% of Spanish EDs, case group) during the first COVID outbreak. They formed control groups of COVID patients without PE and non-COVID patients with PE. Adjusted comparisons for baseline characteristics, acute episode characteristics, and outcomes were made between cases and randomly selected controls (1:1 ratio). The authors identified 368 PEs among 74 814 patients with COVID-19 (4.92‰). The standardized incidence of PE in the COVID population was 310 per 100 000 person-years, significantly higher than that observed in the non-COVID population which was 35 per 100 000 person-years, resulting in an odds ratio (OR) of 8.95. Several characteristics in COVID patients were independently associated with PE, the strongest being D-dimer >1000 ng/mL, chest pain, and chronic heart failure (inverse association). COVID patients with PE differed from non-COVID patients with PE in 16 characteristics, most directly related to COVID infection itself; remarkably, D-dimer >1000 ng/mL, leg swelling/pain, and PE risk factors were significantly less present. PE in COVID patients affected smaller pulmonary arteries than in non-COVID patients, while right ventricular dysfunction (RVD) was similar in both groups.

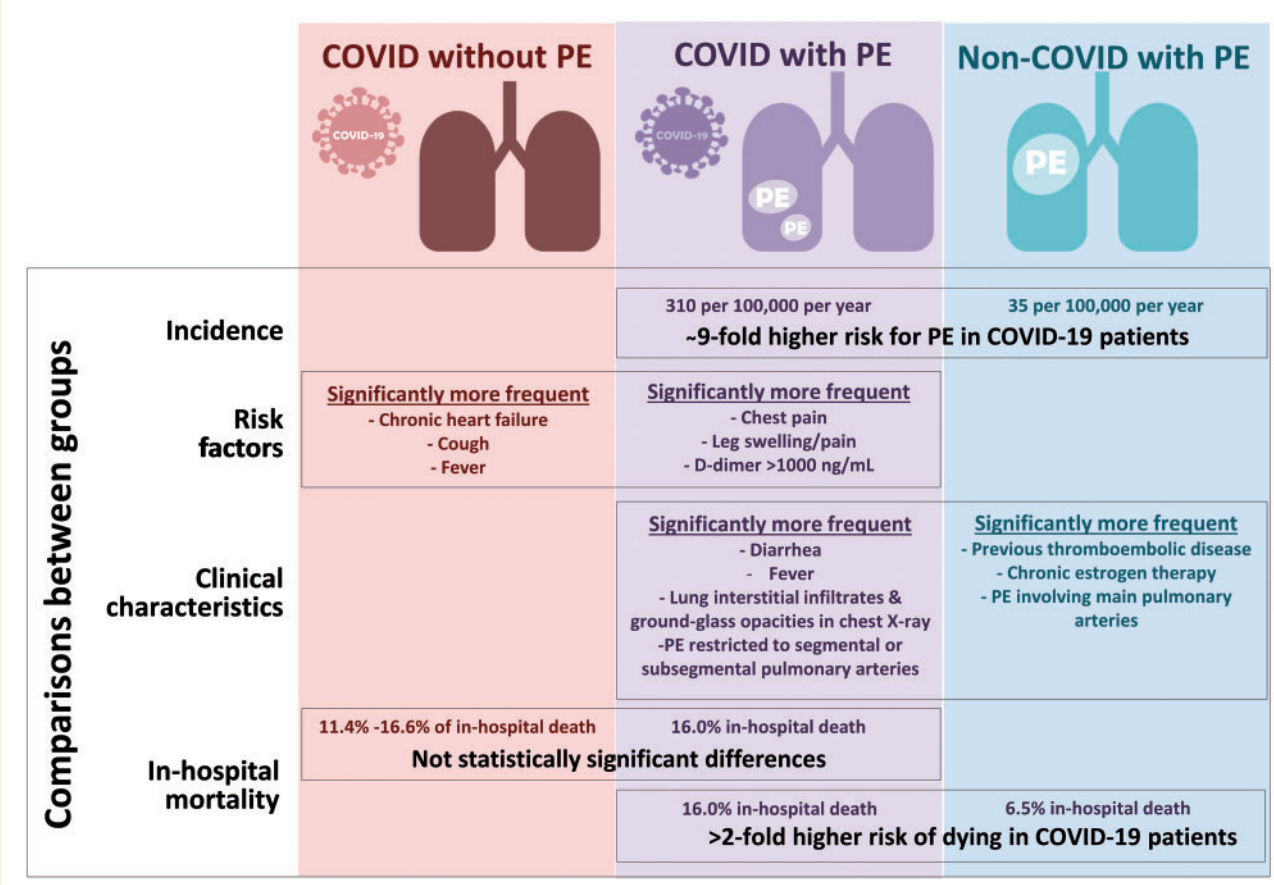

Figure 1 Summary of the results of the study that investigated incidence, risk factors, clinical characteristics, and in-hospital mortality in COVID-19 patients with pulmonary embolism (PE) compared with COVID-19 patients without PE and non-COVID-19 patients with PE (from MiróO, Jimenez S, Mebazaa A, Freund Y, Burillo-Putze G, Martín A, Martín-Sánchez FJ, Lamberechts J, Alquézar-ArbeéA, Jacob J, Llorens P, Piñera P, Gil V, Guardiola J, Cardozo C, Módol Deltell JM, Tost J, Aguirre Tejedo A, Palau-Vendrell A, LLauger García L, Adroher Muñoz M, del Arco Galán C, Agudo Villa T, López-Laguna N, López Díez MP, Beddar Chaib F, Quero Motto E, González Tejera M, Ponce MC, González del Castillo J; Spanish Investigators on Emergency Situations TeAm (SIESTA) network. Pulmonary embolism in patients with COVID-19: incidence, risk factors, clinical characteristics, and outcome. See pages 3127–3142).

In-hospital mortality in COVID patients with PE (16.0%) was like that of COVID patients without PE (16.6%, OR 0.96), but higher than that of non-COVID patients with PE (6.5%, OR 2.74). Adjustment for differences in baseline and acute episode characteristics and sensitivity analysis reported very similar associations (*Figure 1*).

The authors conclude that PE in COVID patients at ED presentation is unusual (~0.5%), but the incidence is ~9-fold higher than in the general (non-COVID) population. Moreover, risk factors and leg symptoms are less frequent, the increase in D-dimer is lower, and emboli involve smaller pulmonary arteries. While PE probably does not increase the mortality of COVID patients, the mortality is higher in COVID than in non-COVID patients with PE. The manuscript is accompanied by an **Editorial** by John Eikelboom and Noel Chan from the Canada and Hamilton General Hospital and McMaster University in Ontario, Canada.[7] The Editorialists conclude that the data provided by Miró and colleagues lend further support to the importance of COVID-19 as a risk factor for venous thrombo-embolism (VTE). At the same time, in the absence of high-quality evidence demonstrating a benefit of therapies that prevent VTE, their finding of a lack of association between PE and death in patients with COVID-19 should prompt further caution in the routine adoption of intensified anticoagulant strategies that can increase bleeding. By reducing blood flow to the lungs, large vessel thrombo-embolism has the potential to worsen respiratory function in patients with COVID-19. However microvascular complications may be the most important thrombo-embolic complications in these patients, and it is unclear if these can be prevented with therapeutic anticoagulation. Consistent with this conclusion, randomized trials of intensified thromboprophylaxis using intermediate or therapeutic doses of anticoagulation have so far failed to demonstrate mortality benefits in a combined total of 4470 hospitalized patients with COVID-19, despite apparently reducing major thrombosis including VTE in some trials. More than 70 randomized trials of antithrombotic therapy are currently ongoing in patients with COVID-19, and their successful completion should help to clarify this issue.

International guidelines suggest home treatment in patients with low-risk acute pulmonary PE, when home circumstances are adequate.[8] However, current evidence is mainly based on cohort

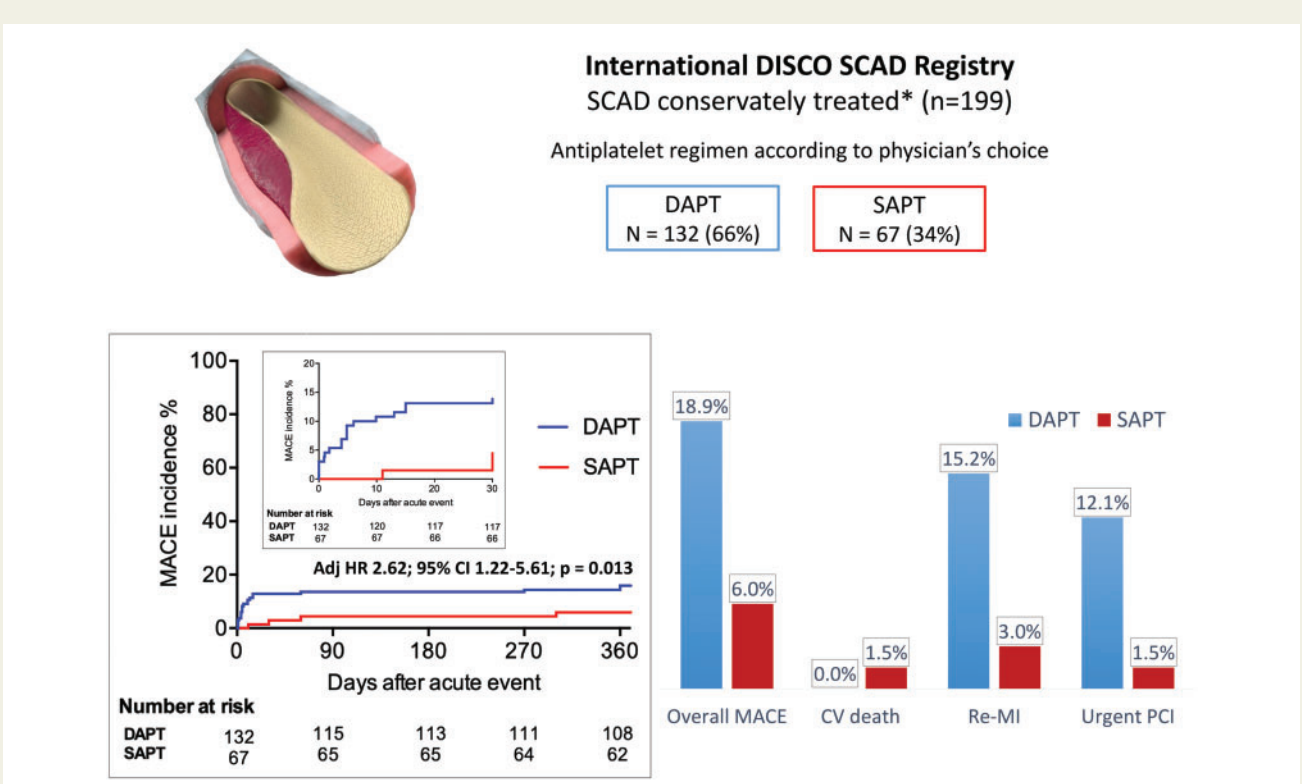

Figure 2 Graphical Abstract (from Cerrato E, Giacobbe F, Quadri G, Macaya F, Bianco M, Mori R, Biolé CA, Boi A, Bettari L, Rolfo C, Ferrari F, Annibali G, Scappaticci M, Pavani M, Barbero U, Buccheri D, Cavallino C, Lombardi P, Bernelli C, D'Ascenzo F, Infantino V, Gambino A, Cinconze S, Rognoni A, Montagna L, Porto I, Musumeci G, Escaned J, Varbella F; DISCO Collaborators. Antiplatelet therapy in patients with conservatively managed spontaneous coronary artery dissection. See pages 3161–3171).

studies using different sets of eligibility criteria. Therefore, controversy persists about the optimal triaging strategy and eligibility criteria for home treatment. In a Clinical Research contribution entitled '**Triaging acute pulmonary embolism for home treatment by Hestia or simplified PESI criteria: the HOME-PE randomized trial**', Pierre-Marie Roy from the CHU Angers: Centre Hospitalier Universitaire d'Angers in France, and colleagues compared the Hestia rule vs. the simplified Pulmonary Embolism Severity Index (sPESI criteria) in triaging patients with acute PE for home treatment.[9] Normotensive patients with PE from 26 hospitals in France, Belgium, the Netherlands, and Switzerland were randomized to triaging either with Hestia or sPESI. They were designated for home treatment if the triaging tool was negative and if the physician in charge, taking into consideration the patient's opinion, did not consider that hospitalization was required. The main outcomes were the 30-day composite of recurrent VTE, major bleeding, or all-cause death (non-inferiority analysis with a 2.5% absolute risk difference as the margin) and the rate of patients discharged home within 24 h after randomization. In the intention-to-treat analysis, 38% of the Hestia patients were treated at home vs. 37% of the sPESI patients, with a 30-day composite outcome rate of 1.3% and 1.1%, respectively. No recurrent or fatal PE occurred in either home treatment arm.

The authors conclude that for triaging PE patients, the strategy based on the Hestia rule and the strategy based on sPESI have similar safety and effectiveness. With either tool complemented by the over-ruling of the physician in charge, more than a third of patients can be treated at home with a low incidence of complications. The manuscript is accompanied by an **Editorial** by Cecilia Becattini from the University of Perugia in Italy and colleagues.[10] The authors highlight that HOME-PE is the largest randomized study assessing home management in patients with acute PE and its results can contribute to the progressive refinement in risk stratification and definition of management pathways for patients with acute PE. Home treatment seems feasible in ~30% of the normotensive patients with acute PE, if adequate patient care is available as an outpatient service. Hestia and sPESI are both able to identify a subgroup of patients with acute PE at low risk for complications, but clinical judgement cannot be completely replaced.

Spontaneous coronary artery dissection (SCAD) is an increasingly diagnosed cause of acute coronary syndrome (ACS), particularly in women. Its real incidence is probably even higher than reported: indeed, it has been underdiagnosed for years due to the lack of modern diagnostic tools (e.g. intravascular imaging) and low awareness of the disease. Observations collected from contemporary SCAD case series have led to the general consensus that conservative therapy should be considered as first-line approach in the absence of clinical high-risk features: dissections can resolve spontaneously over time after conservative management due to recollection of the intimal flap

or resorption of the intramural haematoma.[11–13] The role of antiplatelet therapy in patients with SCAD undergoing initial conservative management is still a matter of debate, with theoretical arguments in favour of and against its use. In a Clinical Research article entitled '**Antiplatelet therapy in patients with conservatively managed spontaneous coronary artery dissection**', Cerrato *et al.* investigated the 1-year outcome of patients with SCAD managed with initial conservative treatment included in the DIssezioni Spontanee COronariche (DISCO) multicentre international registry.[14] Patients were allocated to two groups according to single antiplatelet treatment (SAPT) or double antiplatelet treatment (DAPT) prescription. The primary endpoint was the 12 months incidence of major cardiovascular events (MACE) defined as the composite of all-cause death, non-fatal myocardial infarction (MI), and any unplanned percutaneous coronary intervention (PCI). Out of 314 patients included in the DISCO registry, the authors investigated 199 patients in whom SCAD was managed conservatively. Most patients were female (89%), presented with acute coronary syndrome (ACS; 92%), and mean age was 52.3 years. Sixty-seven (33.7%) were given SAPT whereas 132 (66.3%) received DAPT. Aspirin plus either clopidogrel or ticagrelor were prescribed in 63% and 37% of DAPT patients, respectively. Overall, a 14.6% MACE rate was observed at the 12-month follow-up. Patients treated with DAPT had a significantly higher MACE rate than those with SAPT (18.9% vs. 6.0%, HR 2.62; $P = 0.013$), driven by an early excess of non-fatal MI or unplanned PCI. At multiple regression analysis, type 2a SCAD (OR 3.69; $P = 0.007$) and DAPT regimen (OR 4.54; $P = 0.016$) were independently associated with a higher risk of MACE at 12 months (*Figure 2*).

Cerrato and colleagues conclude that in this European registry most patients with SCAD undergoing initial conservative management received DAPT. Yet, at 1-year follow-up, DAPT, as compared with SAPT, was independently associated with a higher rate of adverse cardiovascular events. This manuscript is accompanied by an **Editorial** by Sharonne Hayes from the Mayo Clinic in Rochester, MN, USA.[15] Hayes concludes that although the relative rarity of SCAD makes development and completion of randomized prospective trials more challenging, the authors' 'counterintuitive' findings should spur us all on to collaborate and be creative in developing an evidence base upon which to inform our approach to early and long-term management of SCAD. Critically we must continue to gather the evidence necessary so that we 'first, do no harm'.

Bleeding risk associated with the potent antithrombotic drugs utilized in ACS is a topic of growing interest.[16–18] Emerging evidence has linked cholesterol metabolism with platelet responsiveness. In a Clinical Research article entitled '**LDL cholesterol levels and in-hospital bleeding in patients on high-intensity antithrombotic therapy: findings from the CCC-ACS Project**', Xin Zhou from the Tianjin Medical University General Hospital in China, and colleagues sought to examine the dose–response relationship between admission LDL cholesterol (LDL-C) and major in-hospital bleeds in ACS patients.[19] Among 42 378 ACS patients treated with PCI enrolled in 192 hospitals in the Improving Care for Cardiovascular Disease in China-ACS project from 2014 to 2019, a total of 615 major bleeds, 218 ischaemic events, and 337 deaths were recorded. After controlling for baseline variables, a non-linear relationship was observed for major bleeds, with a higher risk at lower LDL-C levels. A threshold value of LDL-C <70 mg/dL was associated with an increased risk for major bleeds (adjusted OR 1.49; 95% confidence interval 1.21–1.84) in multivariable-adjusted logistic regression models and in propensity score-matched cohorts. The results were consistent in multiple sensitivity analyses. Among ticagrelor-treated patients, the LDL-C threshold for increased bleeding risk was observed at <88 mg/dL, whereas, for clopidogrel-treated patients, the threshold was <54 mg/dL. Across a full spectrum of LDL-C levels, the treatment effect size associated with ticagrelor vs. clopidogrel on major bleeds favoured clopidogrel at lower LDL-C levels, with no difference at higher LDL-C levels.

The authors conclude that in a nationwide ACS registry, a non-linear association is identified between admission LDL-C levels and major in-hospital bleeds following PCI, with the higher risk at lower levels. The contribution is accompanied by an **Editorial** by Diana Adrienne Gorog from the Imperial College London in the UK, and colleagues.[20] The authors note that while the magnitude of benefit of LDL-C reduction in patients with ACS undergoing PCI should trump concerns over lipid-lowering strategies (the average in-hospital TIMI major bleeding rates were below 1.5% and 2% in the lowest LDL-C categories); in addition, low LDL-C on admission among ACS patients undergoing PCI may be a marker of increased susceptibility to bleeding during intensive antithrombotic therapy. Thus, every effort should be made to reduce the risk of bleeding, including with the use of gastrointestinal prophylaxis, radial rather than femoral artery access, good blood pressure control, anticoagulant or parenteral antiplatelet dosing adjusted to weight and renal function, and careful choice of antithrombotic drugs.

As noted above, patients with acute PE at low risk for short-term death are candidates for home treatment or short hospital stay. In a Meta-analysis article entitled '**Right ventricle assessment in patients with pulmonary embolism at low risk for death based on clinical models: an individual patient data meta-analysis**', Cecilia Becattini from the University of Perugia in Italy, and colleagues aimed at determining whether the assessment for RVD or elevated brain natriuretic peptide (BNP)/N-terminal proBNP (NT-proBNP) improves identification of low-risk patients compared with clinical models alone.[21] Individual patient data meta-analysis of studies assessing the relationship between RVD or elevated troponin and short-term mortality in patients with acute PE at low risk for death based on clinical models (PESI, sPESI, or Hestia). The primary study outcome was short-term death defined as death occurring in hospital or within 30 days. Individual data of 5010 low-risk patients from 18 studies were pooled. Short-term mortality was 0.7%. RVD at echocardiography, computed tomography, or BNP/NT-proBNP was significantly associated with increased risk for short-term death (1.5 vs. 0.3%; OR 4.81), death within 3 months (1.6 vs. 0.4%; OR 4.03), and PE-related death (1.1 vs. 0.04%; OR 22.9).

The authors conclude that RVD should be considered to improve identification of low-risk PE patients. The manuscript is accompanied by an **Editorial** by Marc Humbert from the Université Paris-Saclay in France.[22] Humbert and colleagues conclude that Becattini and colleagues provide more evidence to solve a frequently encountered clinical dilemma. A patient with acute PE classified as being at low risk for death, but with abnormal cardiac biomarkers or morphological right ventricular findings, should be managed as an intermediate-risk PE patient, as suggested by the most recent update of the ESC guidelines. The prognosis of low-risk patients with no cardiac involvement

is excellent, which should allow outpatient management to be considered as frequently as possible, subject to a well-organized care pathway.

The Issue is also complemented by two Discussion Forum contributions. In a commentary entitled '**Single antiplatelet therapy after TAVI: clarity on existing data**', George Dangas from the Icahn School of Medicine at Mount Sinai in New York, USA and colleagues comment on the recent publication '**Management of antithrombotic therapy in patients undergoing transcatheter aortic valve implantation: a consensus document of the ESC Working Group on Thrombosis and the European Association of Percutaneous Cardiovascular Interventions (EAPCI), in collaboration with the ESC Council on Valvular Heart Disease**' by Jurrien ten Berg from the The Cardiovascular Research Institute Maastricht (CARIM) in Maastricht, the Netherlands, and colleagues.[23,24] ten Berg *et al.* respond in a separate comment.[25]

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

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