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EDITORIAL

Focus on cardiovascular management in critically ill patients

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Assessment and management of the cardiovascular system are continuous tasks in the ICU, and since most interventions carry potential benefits as well as potential harms, additional data are of paramount importance to inform treatment. With this paper, we aim to summarize the latest evidence on cardiovascular management from recent publications.

The risk of venous thromboembolisms (VTEs) in critically ill patients prompts ICU clinicians to prescribe pharmacologic prophylaxis that requires the risk of thrombosis to be balanced against an increased risk of bleeding. Direct oral anticoagulants (DOACs) are used outside the ICU as an alternative to warfarin in thromboprophylaxis but may pose a challenge in the ICU because of uncertain activity and risk of accumulation from organ failure [1]. The APEX trial randomized acutely ill patients to VTE prophylaxis with the low molecular weight heparin (LMWH) enoxaparin or an extended-duration DOAC (betrixaban) [2]. A post hoc analysis of the 703 ICU patients in the trial indicated decreased risk of thromboembolic events, but increased risk of non-major bleeding with DOAC [3]. Although this post hoc study of ICU patients suggested a net benefit with DOAC, LMWH should not be abandoned until the results are established in randomised clinical trials (RCTs) specifically designed for ICU patients [4]. Even if evidence for one class of drugs for VTE prophylaxis would emerge, implementing the change may not be straightforward. Based on data suggesting benefit of LMWH over unfractionated heparin (UFH), a multicomponent intervention tailored to individual ICUs to increase the use of LMWH over unfractionated heparin for VTE prophylaxis was studied in a pre-post trial across 11 Canadian ICUs [5] (Table 1). While the intervention was successful with a substantial increase in use of LMWH compared to the control ICUs, considerable resources were needed to change everyday practice. A non-pharmacologic intervention aiming at preventing pulmonary embolism has recently been tested in a clinical trial, where 240 patients with severe trauma and contraindication to prophylactic anticoagulation were randomised to either insertion of a retrievable vena cava filter or no filter [6]. The results of the trial suggested no overall benefit with the use of vena cava filters, and considering the potential harms and the cost, there is a limited role of prophylactic vena cava filters in these patients.

Thromboembolism and VTE prophylaxis in ICU patients with atrial fibrillation (AF) are of particular concern, especially in new-onset AF with haemodynamic stability. New-onset AF has been associated to adverse outcomes in several studies and is likely frequent in the ICU, but valid estimates of its incidence are missing [7]. Causality cannot be inferred given residual confounding (e.g. sicker patients tend to develop new-onset AF) and the interventions in ICU against AF may even drive adverse outcomes. These interventions include rhythm control, rate control and prophylaxis, each with an overall low or very low quality of supporting evidence [7].

Haemodynamic evaluation in the ICU is mainly targeted to assess the adequacy of cardiac output using a battery of tests and measurements ranging from simple non-invasive variables (e.g. heart rate) to highly invasive measurements (e.g. using a pulmonary artery catheter). Clinical examination includes several readily available markers of haemodynamic compromise, but the comparable validity of these signs is less studied. In a Dutch large prospective single-centre study, the ability of 19 standardised clinical findings to estimate cardiac index

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Table 1 Design, findings and limitations of recent studies on cardiovascular management

Study	Aims and design	Main findings	Limitations
Stelfox et al. [5]	To assess a multicomponent intervention encouraging the use of over UFH for VTE prophylaxis in critically ill patients Multicentre pre-post trial study in 11 ICUs (5 intervention and 6 control ICUs)	12,342 patients included Increased use of LMWH in intervention ICUs vs. control (from 45.9 to 78.3% vs. 37.9 to 53.3%) No change in clinical outcomes	Not randomised (ICUs allocated according to geography) Risk of residual confounding Decreased power to detect clinical outcome differences due to cross-over effect
Ho et al. [6]	To assess the safety and efficacy of vena filters in patients with severe trauma and contraindication to anticoagulative therapy Multicentre randomised clinical trial in 4 hospitals	240 patients randomised Similar rates of combined primary endpoint of pulmonary embolism or death within 90 days, 13.9% in the cava filter group vs. 14.4% in the control group (HR, 0.99; 95% CI 0.51 to 1.94)	Underpowered for primary endpoint Lack of blinding with risk of influencing management of anticoagulative therapy after randomisation Vast majority of patients included in one hospital
Hiemstra et al. [8] (SICS-I study)	To assess the diagnostic performance of 19 variables obtained in a standardised clinical examination for estimation of cardiac index measured by ultrasonography Prospective single centre observational study	1,075 patients included Seven clinical examination findings independently associated with decreased cardiac index Combined in multivariable analysis, their AuROC was 0.74 (95% CI 0.70–0.78)	Ultrasonography not gold standard for cardiac index Limited generalisability due to single centre design
Janz et al. [11] (PrePARE trial)	To assess administration of an intravenous fluid bolus to prevent cardiovascular collapse during intubation of critically ill adults Multicentre randomised trial with 1:1 allocation to either 500 ml crystalloid bolus or no fluid bolus	337 patients randomised Similar rates of cardiovascular collapse, 20% in the fluid bolus group vs. 18% in the no fluid bolus group (ARD, 1.3%; 95% CI − 7.1 to 9.7%)	Not blinded Stopped early due for futility but results compatible with almost 10% ARD Only 17% of patients with vasopressor support prior to intubation
May et al. [14]	To assess the between-centre variation in functional outcomes after OHCA Observational study from International Cardiac Arrest Registry from 42 hospitals	3,855 patients included A wide variation in centre-specific standardized rates for good functional outcome across centres was observed (from 0.47 [0.37–0.58] to 0.20 [0.12–0.26]). High-performing centres had shorter time to TTM and higher rates of PTCA and use of prognostication tools in comatose patients than low-performing centres	Risk of residual confounding, including confounding by indication and competing risks Causality cannot be inferred for the observed differences in treatment and prognostic test use
Nordberg et al. [15] (PRINCESS trial)	To assess prehospital trans-nasal evaporative intra-arrest cooling vs. standard practice where cooling was initiated after hospital arrival for neurologic outcome in patients with witnessed OHCA Multicentre randomised clinical trial in 11 EMS services	677 patients randomised Similar proportions of patients with good neurological outcome (16.6% in the intervention group vs. 13.5% in the control group; RR, 1.23; 95% CI 0.86–1.72)	Potentially underpowered to detect clinically important differences due to lower event rates of primary outcome than anticipated
Lascarrou et al. [16] (HYPERION trial)	To assess neurological outcome in moderate therapeutic hypothermia (33 °C) compared with targeted normothermia (37 °C) in patients who were comatose after cardiac arrest with non-shockable rhythm Multicentre randomised clinical trial in 25 ICUs	584 patients randomised More patients with favourable neurological outcome at 90 days in the hypothermia group compared with the normothermia group; 10.2% vs. 5.7% (ARD, 4.5%; 95% CI 0.1–8.9%)	Substantial number of patients with temperature above 38 °C in the control group Small absolute difference in primary outcome between experimental and control group (fragility index = 1) Primary outcome was assessed by telephone interview

ARD Absolute risk difference, *AuROC* Area under the receiver-operator characteristics curve. *CI* Confidence interval, *EMS* emergency services, *HR* Hazard ratio *ICU* Intensive Care Unit, *LMWH* Low-molecular-weight heparin, *OHCA* Out-of-hospital cardiac arrest, *TTM* targeted temperature management, *UFH* Unfractionated heparin, *VTE* Venous thromboembolism

was investigated using transthoracic echocardiography as reference [8]. Interestingly, capillary refill time and peripheral to central temperature gradient outperformed central venous pressure and urinary output, which were not associated with changes in cardiac index. In a multivariate analysis of the best performing variables from the clinical examination, the model had an area under the curve of 0.74 (95% CI 0.70–0.78), indicating a reasonable, but not good discrimination [8].

Clinical examination has been proposed to serve as a trigger for further haemodynamic evaluation with cardiac ultrasonography rather than a substitute of it [9]. The circulatory assessment is typically used to guide fluid administration to increase cardiac index. A recent ESICM taskforce on fluid administration in circulatory dysfunction considered clinical signs of hypoperfusion important in the assessment of both the indication for and efficacy of a fluid challenge [10]. A cautious approach to fluid administration in absence of signs of cardiovascular collapse was supported by the findings of the PrePARE trial where 337 critically ill patients requiring tracheal intubation were randomly assigned to either a prophylactic fluid bolus or no fluid bolus [11]. The trial was stopped early for futility as there were no apparent differences in the rates of cardiovascular collapse upon induction between the two groups. Even when cardiac output increases in response to fluid administration, the balance between benefit and harm is not obvious and fluid management in the critically ill will likely remain controversial until many knowledge gaps are closed [12].

Beyond early cardiopulmonary resuscitation and defibrillation, there are data suggesting that some recommended advance life support interventions may not always represent the best strategy in cardiac arrest [13]. Observational data suggest centre-specific differences in outcomes and treatments after out-of-hospital cardiac arrest (OHCA) not explained by patient characteristics indicating that clinical practice needs further exploration [14]. One of the differences between low- and high performing centres were the handling of targeted temperature management (TTM), including time to start of TTM. Interestingly, however, in the PRINCESS trial, an earlier start of TTM with early pre-hospital trans-nasal evaporative cooling did not result in improved neurological outcome after OHCA compared with cooling after hospital arrival [15]. TTM may, though, gain renewed popularity following the results of the HYPERION trial which suggested improved neurological outcome with moderate therapeutic hypothermia (33 °C) compared with targeted normothermia (37 °C) in comatose patients after cardiac arrest with non-shockable rhythm [16].

In summary, cardiovascular management in ICU often requires the benefits and harm of each intervention to be carefully balanced in each specific patient. Additional clinical trials are much needed to make the balancing act steadier.

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Compliance with ethical standards

Conflicts of interest
Dr. Hjortrup reports that the Dept. of Intensive Care, Rigshospitalet receives support for research from Ferring Pharmaceuticals and the Novo Nordisk Foundation. Dr. Sandroni and Dr. Aneman have none relevant conflicts of interest to declare.

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