


Current and novel biomarkers in cardiogenic shock

Victor Galusko¹, Florian A. Wenzl^{2,3,4,5}, Christophe Vandenbriele^{1,6}, Vasileios Panoulas^{1,7}, Thomas F. Lüscher^{1,2,7,8†}, and Diana A. Gorog^{1,8,9*†}

¹Royal Brompton and Harefield Hospitals, Guy's and St. Thomas' NHS Foundation Trust, London, UK; ²Centre for Molecular Cardiology, University of Zurich, Schlieren, Switzerland; ³National Disease Registration and Analysis Service, NHS, London, UK; ⁴Department of Cardiovascular Sciences, University of Leicester, Leicester, UK; ⁵Department of Clinical Sciences, Karolinska Institutet, Stockholm, Sweden; ⁶Heart Center, OLV Hospital, Aalst, Belgium; ⁷Faculty of Medicine, National Heart and Lung Institute, Imperial College, London, UK; ⁸School of Cardiovascular Medicine and Sciences, Kings College London, London, UK; and ⁹School of Life and Medical Sciences, Postgraduate Medical School, University of Hertfordshire, Hertfordshire, UK

Received 3 April 2024; revised 11 October 2024; accepted 29 October 2024

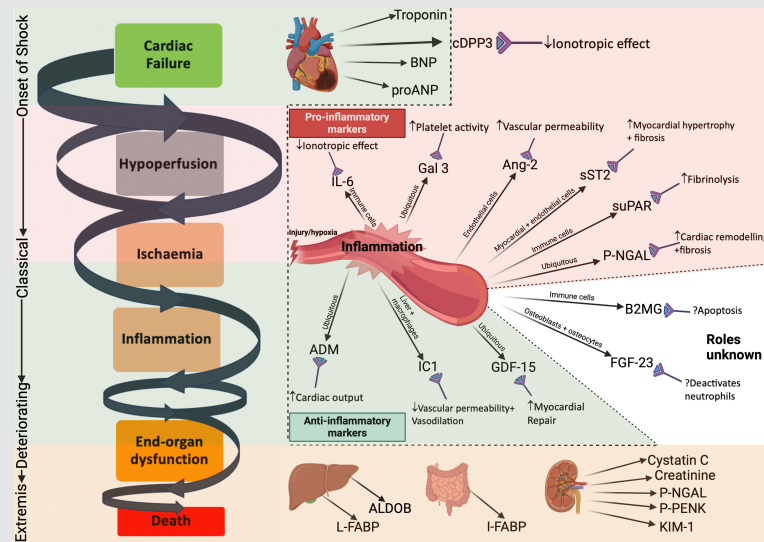
Cardiogenic shock (CS) carries a 30–50% in-hospital mortality rate, with little improvement in outcomes in the last decade. Challenges in improving outcomes are closely linked to the frequent late presentation or diagnosis of CS where the ‘point of no return’ has often passed, leading to haemodynamic dysregulation, progressive myocardial depression, hypotension, and a downward spiral of hypoperfusion, organ dysfunction and decreasing myocardial function, driven by inflammation and metabolic derangements. Novel therapeutic interventions may have varying efficacy depending on the type and stage of shock in which they are applied. Biomarkers that aid prediction and early detection of CS, provide early signs of organ dysfunction and define prognosis could help optimize management. Temporal change in such biomarkers, particularly in response to pharmacological interventions and/or mechanical circulatory support, can guide management and predict outcome. Several novel biomarkers enhance the prediction of mortality in CS, compared to conventional parameters such as lactate, with some, such as adrenomedullin and circulating dipeptidyl peptidase 3, also able to predict the development of CS. Some biomarkers reflect systemic inflammation (e.g. interleukin-6, angiotensin 2, fibroblast growth factor 23 and suppressor of tumorigenicity 2) and are not specific to CS, yet inform on the activation of important pathways involved in the downward shock spiral. Other biomarkers signal end-organ hypoperfusion and could guide targeted interventions, while some may serve as novel therapeutic targets. We critically review current and novel biomarkers that guide prediction, detection, and prognostication in CS. Future use of biomarkers may help improve management in these high-risk patients.

.....

*Corresponding author. National Heart and Lung Institute, Imperial College, Dovehouse St, London SW3 6LY, UK. Tel: +44 207 0348841, Email: d.gorog@imperial.ac.uk

†Joint senior authors.

Graphical Abstract



A summary of current and novel biomarkers and their potential stages of release in cardiogenic shock. The diagram illustrates the proposed release of the biomarkers during the different stages of cardiogenic shock: progression from cardiac dysfunction/stress, through to inflammation and end-organ dysfunction. It is believed that a self-propagating spiral of events follows as a result of hypoperfusion, ischaemia and inflammation, leading to end-organ dysfunction. ADM, adrenomedullin; Ang-2, angiotensin-2; ALDOB, aldolase B; B2MG, beta-2-microglobulin; BNP, brain natriuretic peptide; cDPP3, circulating dipeptidyl peptidase 3; FGF-23, fibroblast growth factor 23; Gal-3, galectin 3; GDF-15, growth differentiation factor 15; I-FABP, intestinal fatty acid binding protein; IC1, C1 inhibitor protein; IL-6, interleukin-6; KIM-1, kidney injury molecule-1; L-FABP, liver fatty acid binding protein; P-NGAL, plasma neutrophil gelatinase-associated lipocalin; P-PENK, plasma proenkephalin; proANP, pro-atrial natriuretic peptide; sST2, soluble suppressor of tumorigenicity 2; suPAR, soluble urokinase-type plasminogen activator receptor.

Keywords

Acute myocardial infarction • Acute heart failure • Cardiogenic shock • Biomarkers • Mechanical circulatory support

Introduction

Cardiogenic shock (CS) remains a major cause of morbidity and mortality in patients with acute coronary syndrome (ACS) and acute heart failure (HF).¹ Traditionally defined as ineffective cardiac output due to primary cardiac dysfunction, resulting in inadequate end-organ perfusion, the Society for Cardiovascular Angiography and Interventions (SCAI) has more recently delineated different gradations of CS.^{2,3}

The high mortality rate associated with CS has not improved significantly over the last few decades.^{4,5} In-hospital mortality remains at 30–50%, and of those patients surviving until discharge, about 48% are readmitted and 15% die within a year.^{4,6} Treatment options are limited, and plagued by a failure of treatments to disrupt the complex downward spiral, once CS sets in.^{3,7}

The pathophysiological mechanisms underlying the shock spiral are incompletely understood, although dysfunctional regulatory pathways are likely involved. Endothelial responses that are initially protective become harmful. Vasoconstriction, initiated

by activation of the sympathetic nervous system, is eventually reversed by β -adrenergic receptor downregulation and inflammation, due to activation of nucleotide-binding oligomerization domain-like receptor protein 3 inflammasome and interleukins (IL), leading to inappropriate vasodilation. Expression of inducible nitric oxide synthase results in an increase in levels of nitric oxide and reactive oxygen species, leading to the production of cytotoxic products.⁸ This results in negative inotropic effects, suppression of mitochondrial function, inflammation and reduced catecholamine responses, ultimately leading to vasodilation.⁹

Biomarkers have emerged as indicators of poor outcome and potential novel therapeutic targets. In order to incorporate novel biomarkers into early identification, monitoring, prognostication and treatment of patients with CS, it is necessary to understand their origins, the biological pathways and interactions, and their time course in CS. Previous efforts to summarize biomarkers in CS have been brief, often lacking detailed exploration of all biomarkers, their pathophysiological mechanisms, and comparative diagnostic usefulness.^{10–12} Furthermore, an overview of the usefulness of

these biomarkers in the context of mechanical circulatory support (MCS) is not described. Here, we aim to bridge this gap by summarizing current and novel biomarkers, discussing their merits and limitations, and identifying potential future avenues for research.

Currently available biomarkers

Biomarkers are frequently incorporated into clinical scores for the risk stratification of patients with CS. Over 30 risk scores are currently available and incorporate a number of plasma biomarkers, including pH, lactate, creatinine, liver function tests, brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP).^{13,14} All these markers are associated with increased mortality in Yes CS (Table 1). Many also feature in the SCAI risk stratification system, designed to predict CS outcomes and aid inter-hospital communication.²

Lactate and pH are markers of tissue hypoperfusion resulting from anaerobic respiration and eventually tissue acidosis. Although lactate is highly predictive of in-hospital mortality and readily available as a point-of-care test, it is not specific for CS, being also elevated as a consequence of impaired clearance, as seen in liver dysfunction and chronic kidney disease (CKD), drug interactions (e.g. metformin), or as a consequence of administration of high-dose catecholamines.⁶⁹ Lactate clearance may be a better predictor of mortality than circulating lactate level, especially in patients on MCS.^{17,69,70} Other studies indicated that an 8-h lactate is superior to lactate clearance for the prediction of 30-day mortality in CS.^{18,19} The optimal time to measure lactate to predict prognosis remains unclear, especially as a single 8-h value likely reflects lactate clearance. The prognostic value of lactate may decline over time, and is potentially affected by inotropic and renal replacement therapies.^{19,71} Despite these limitations, lactate is used routinely in the assessment of CS.

Both BNP and NT-proBNP are elevated in CS, due to increased left ventricular (LV) filling pressures and are highly predictive of hospitalization and mortality.^{72,73} Despite being included in several risk scores, the evidence supporting the usefulness of BNP in CS is mixed. Indeed, in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), a large registry of patients with end-stage and acute HF treated with LV assist device (LVAD) support, BNP was elevated, but did not correlate with mortality or major adverse cardiovascular events (MACE).⁴⁵ Both BNP and NT-proBNP levels are affected by renal clearance, accounting for some of the observed variability.⁶⁶ Importantly, in a head-to-head comparison, adrenomedullin (ADM), IL-6 and procalcitonin (PCT) all outperformed BNP in predicting CS mortality.^{38,46,74}

In a prospective study of 273 patients with CS, half of whom had ACS, elevated troponin levels, reflecting greater myocyte loss, were a better predictor of 30-day mortality than NT-proBNP,³⁴ and are associated with unsuccessful weaning from veno-arterial extracorporeal membrane oxygenation (V-A ECMO).^{34,61,75}

The systemic inflammation that ensues in CS leads to an increase in white cell count and cytokine release.⁷⁶ In patients with coronary artery disease, raised PCT levels are associated with MACE, and

are a better predictor of all-cause mortality in CS than C-reactive protein (CRP).^{38,76,77} Inflammation and stress can result in hyperglycaemia.⁷⁸ While diabetes in itself is a risk factor for CS, impaired fasting glucose and raised random glucose levels are adverse markers only in patients without a prior history of diabetes.^{28,29}

Current biomarkers are widely available and in use, but are non-specific and have limitations, namely low sensitivity and specificity (Table 1).

Novel biomarkers

A number of novel biomarkers, reflecting the dysfunction of different organ systems, are released into the circulation during the various phases of CS (Graphical Abstract). The physiological or pathological mechanisms through which novel biomarkers reflect the development of or influence the outcome of CS are not fully understood, although some have tried to shed light on this.⁷⁹ Some biomarkers are released as a result of cellular injury (Figure 1), while others are released as part of the inflammatory response that ensues (Figure 2). Most of the biomarkers discussed below are measurable in blood plasma, unless stated otherwise, and are summarized in Table 2. All these novel biomarkers can guide prognosis, but some also predict the onset of CS and mortality, while others forecast end-organ dysfunction. As CS progresses and necessitates MCS, certain biomarkers have been shown to predict recovery, complications of, and ease of weaning from MCS (Figure 3).

Novel biomarkers predicting onset of cardiogenic shock

Adrenomedullin

Adrenomedullin (ADM), originally isolated from the adrenal medulla, is expressed by all tissues, including endothelial and smooth muscle cells and fibroblasts.¹⁴⁰ ADM is a vasoactive peptide produced from a multistep proteolytic cleavage of prepro-ADM. This process also generates adrenotensin and a pro-ADM N-terminal 20 peptide (PAMP), which themselves are vasoactive (PAMP exerts vasodilatory effects, whereas adrenotensin is vasoconstrictive).¹⁴¹ Myocardial stunning and ischaemia lead to increased LV filling pressures, triggering a neurohumoral response involving catecholamines, aldosterone and angiotensin II, that all further stimulate ADM production.^{71,142} The inflammatory response that ensues (involving IL-1 and tumour necrosis factor- α) further stimulates ADM production.¹⁴³

Besides being a powerful predictor of adverse outcome in patients with ACS and acute HF, ADM outperforms troponin, BNP and CRP in predicting 30-day mortality.^{142,144}

However, in a recent substudy of the STRONG-HF trial enrolling 1005 patients, both ADM and NT-proBNP showed similar area under the curve (AUC) for predicting 180-day all-cause mortality or HF rehospitalization.¹⁴⁵ In patients hospitalized with suspected ST-elevation myocardial infarction (STEMI), the non-biologically active precursor, mid-regional pro-ADM (MR-proADM), was independently predictive of CS, with an AUC of 0.82.⁸⁴ Biologically

Table 1 Current biomarkers used in the risk stratification of cardiogenic shock

Current biomarkers	Studies + (patient n=)	Aetiology of CS	Highest AUC for mortality (95% CI)	Investigated timing of biomarker	Cardiac specific?	Goes up in sepsis?	Goes up in malignancy?	Predicts onset of CS	Predicts mortality
pH [H ⁺] ¹⁵	Studies = 1 CS Patients = 1782	ACS, HF	-	On admission	No	Yes	No	N/A (potentially ¹⁵)	Yes
Lactate ^{17,18,19,20,21,15,22,26}	Studies = 12 CS Patients = 3912	ACS, HF, valvular, post-cardiomy	30-day mortality = 0.69 30-day mortality = 0.76 30-day mortality = 0.81 In hospital mortality = 0.79 30-day mortality = 0.65	On admission At 8-h At 24-h Lactate clearance at 24 h On admission	No No No No	Yes Yes Yes ¹ Yes	Yes ^{2,7} Yes ² Yes ² Yes	Yes Yes N/A N/A	Yes Yes Yes AKI is a strong risk factor for mortality
Glucose ^{28,29,30,31,32}	Studies = 5 CS Patients = 2555 Studies = 1 CS Patients = 190	ACS, HF	30-day mortality and/or RRT = 0.79	Day 3	No	Yes	Yes ² Yes	N/A N/A	Yes AKI is a strong risk factor for mortality
Creatinine ^{33,4}	Studies = 2 CS Patients = 258 Studies = 5 CS Patients = 753	ACS, HF, valvular, post-cardiomy	1-year mortality = 0.80 30-day mortality = 0.67 (0.60–0.74)	Day 3 On admission	Yes	Yes ³⁶	Yes ^{3,7} Yes ^{4,4}	Yes N/A	Yes Yes
Troponin ^{34,5}	Studies = 2 CS Patients = 258 Studies = 5 CS Patients = 753	ACS, HF, valvular, post-cardiomy	30-day mortality = 0.66	On admission	No	Yes ⁴³	Yes ^{4,4} Yes ⁹	N/A N/A	Yes Yes
Procalcitonin ^{3,8,39,40–42}	Studies = 4 + 1 CS Patients = 410 + 7290	ACS, myocarditis	30-day mortality = 0.85 30-day mortality = 0.561	At 24-h On admission	Yes	Yes ⁴⁸	Yes ⁹	N/A	Yes
proBNP ^{1,3,38,45,46,47}	Studies = 4 + 1 CS Patients = 410 + 7290	ACS, HF, valvular, post-cardiomy	30-day mortality = 0.71	At 24-h	Yes	Yes ⁴⁸	Yes ⁹	N/A	Yes

Current biomarkers	Brain	Heart	Lung	Renal	Liver	Intestine	Haematologic/bleeding	MCS
pH [H ⁺] ¹⁵	N/A (potentially ⁵⁰)	Yes	N/A	Yes	Yes	Yes	N/A (potentially ⁵¹)	Predicts mortality on ECMO/MCS
Lactate ¹⁷	Yes	Yes	N/A (potentially ⁴⁵)	N/A (potentially ⁴⁶)	N/A (potentially ⁴⁷)	N/A (potentially ⁴⁷)	N/A (potentially ⁵¹)	Predicts weaning off ECMO
Glucose ²⁸	N/A	Yes	N/A (potentially ⁴⁵)	N/A (potentially ⁴⁶)	N/A (potentially ⁴⁷)	N/A	N/A (potentially ⁵¹)	Predicts weaning off MCS
Creatinine ^{33,4}	N/A	N/A	Yes	N/A (potentially ⁴⁶)	N/A (potentially ⁴⁷)	N/A	N/A (potentially ⁵¹)	Yes ⁵²
Troponin ³⁴	N/A	Yes	N/A (likely ⁴⁹)	N/A (potentially ⁴⁶)	N/A (potentially ⁴⁷)	N/A	N/A	Yes ⁵²
Procalcitonin ⁴⁰	N/A	Yes	N/A (potentially ⁴⁵)	N/A (potentially ⁴⁶)	N/A (potentially ⁴⁷)	N/A	N/A	Yes
proBNP ³⁸	N/A	Yes	N/A (potentially ⁴⁵)	N/A (potentially ⁴⁶)	N/A (potentially ⁴⁷)	N/A	Yes	Yes
								Unlikely ¹⁵

The table summarizes their predictive abilities in CS, their correlation with end-organ dysfunction and whether their use has been studied in the context of MCS. As concurrent diseases (such as sepsis and malignancy) may confound CS state, some of the biomarkers also increase in these conditions.

The table is colour coded according to whether this information is available – Yes; No; No evidence available.

ACS, acute coronary syndrome; AKI, acute kidney injury; AUC, area under the curve; CI, confidence interval; CS, cardiogenic shock; ECMO, extracorporeal membrane oxygenation; HF, heart failure; LC, lactate clearance; MCS, mechanical circulatory support; N/A, not available; NRI, net reclassification improvement; proBNP, pro-B-type natriuretic peptide.

^aAlthough creatinine is frequently used in the definition of AKI, which is a risk factor for mortality in CS, few studies examine the direct effect of creatinine on mortality in CS. A comprehensive review of AKI in CS can be found here.⁴⁸

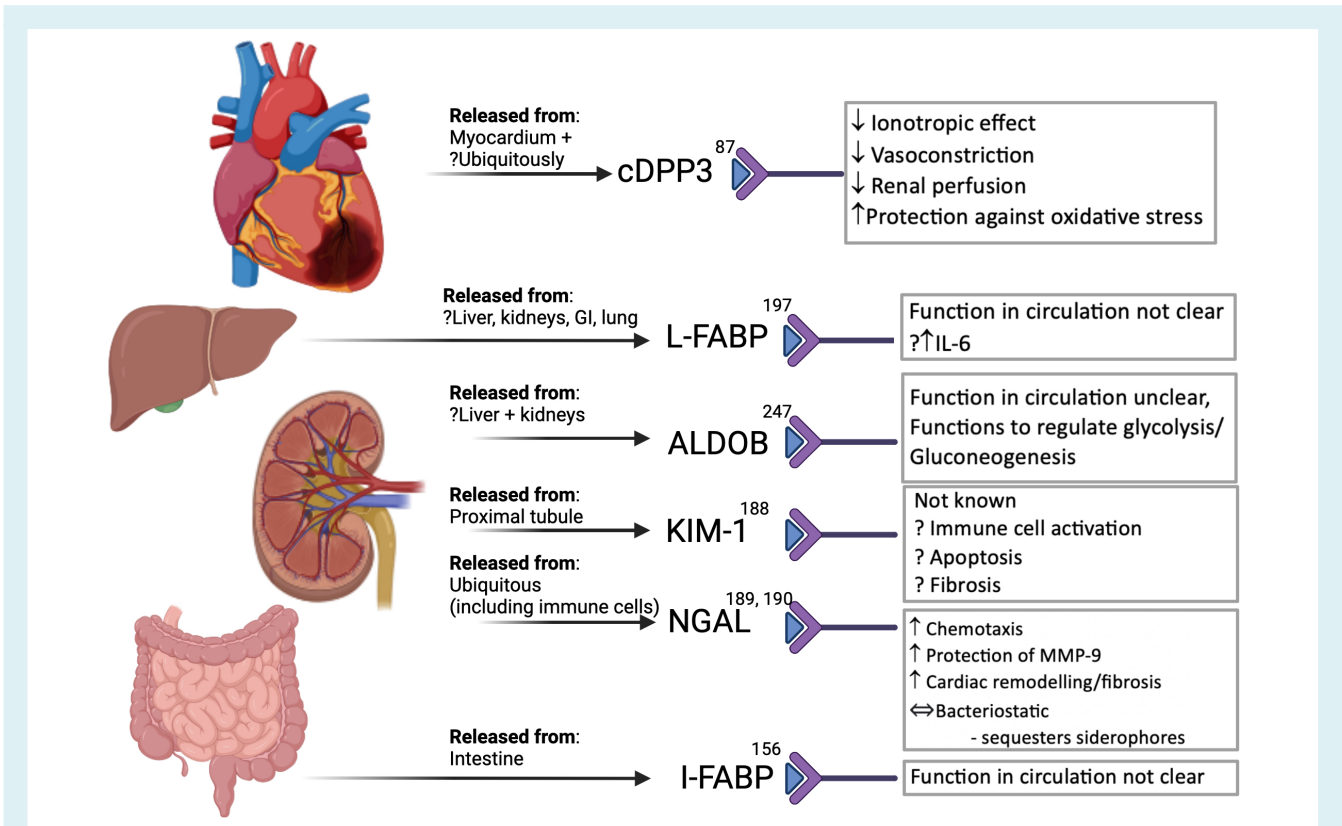


Figure 1 Summary of molecules released as a consequence of cellular damage in cardiogenic shock and their potential downstream effects in the circulation. Tissue injury occurs as a consequence of ischaemia and results in the release of molecules that have been associated with poor prognosis in cardiogenic shock. They have differing roles in the circulation, however we only have a limited understanding of their effects, especially in cardiogenic shock. cDPP3 has emerged as an important prognostic molecule in cardiogenic shock recently, and in a mouse model, it has a direct negative effect on the myocardium and kidneys. ALDOB, aldolase B; cDPP3, circulating dipeptidyl peptidase 3; GI, gastrointestinal; I-FABP, intestinal fatty acid binding protein; IL-6, interleukin-6; KIM-1, kidney injury molecule-1; L-FABP, liver fatty acid binding protein; MMP-9, matrix metalloproteinase-9; NGAL, plasma neutrophil gelatinase-associated lipocalin.

active ADM showed increasing prognostic value from 48 h post-diagnosis and beyond, with AUC 0.71 at 48 h and 0.80 at 5–10 days.⁷¹ It has been used to predict 30-day, 90-day and 1-year mortality in ACS patients with CS, and improves the prediction of CS when added to risk scores such as the Observatoire Régional Breton sur l'Infarctus (ORBI) or CardShock.^{71,46,146} ADM correlates with haemodynamic indices including reduced cardiac index, mean arterial pressure, central venous pressure, and systolic pulmonary artery pressure, alongside markers of end-organ dysfunction.⁷¹ Furthermore, high ADM levels at or beyond 48 h correlate with persistently impaired LV function and decreased vasopressor responsiveness in sepsis.^{71,147,148}

Circulating dipeptidyl peptidase 3

Dipeptidyl peptidase 3 (DPP3) is a ubiquitously expressed enzyme, digesting several oligopeptides including angiotensins, enkephalins and endorphins.¹⁴⁹ Upon cell death, this zinc-dependent metalloproteinase is released into the circulation, where elevated levels have been measured in cardiogenic, septic and haemorrhagic shock.¹⁵⁰

Elevated circulating DPP3 (cDPP3) levels are associated with increased mortality in CS and are predictive of the development of in-hospital CS.^{87,151} Addition of cDPP3 level to the ORBI risk score improved the discrimination and reclassification value for developing in-hospital CS (net reclassification improvement [NRI] 0.255, $p=0.01$).⁸⁷ Furthermore, the addition of cDPP3 to the GRACE 2.0 score improved discrimination and reclassification of 30-day and 1-year mortality with NRI 0.125 and 0.347, respectively.⁸⁷

In a substudy comparing noradrenaline and adrenaline support in 57 patients with CS, cDPP3 correlated with reduced cardiac index, lower estimated glomerular filtration rate (eGFR) and a higher Simplified Acute Physiology Score II.¹⁵¹ Similarly, in a small prospective study of 15 patients, high cDPP3 levels correlated with pulmonary hypertension, reduced stroke volume and the need for mechanical ventilation.¹⁵²

In a large, prospective, multicentre cohort study of 4787 patients with ACS, cDPP3 on admission was predictive of the development of CS, and was superior to conventional markers such as troponin and NT-proBNP.^{87,153,154} In a subgroup of 12 patients who underwent cardiac magnetic resonance imaging, cDPP3 level was associated with infarct size.⁸⁷ Persistently elevated cDPP3 levels

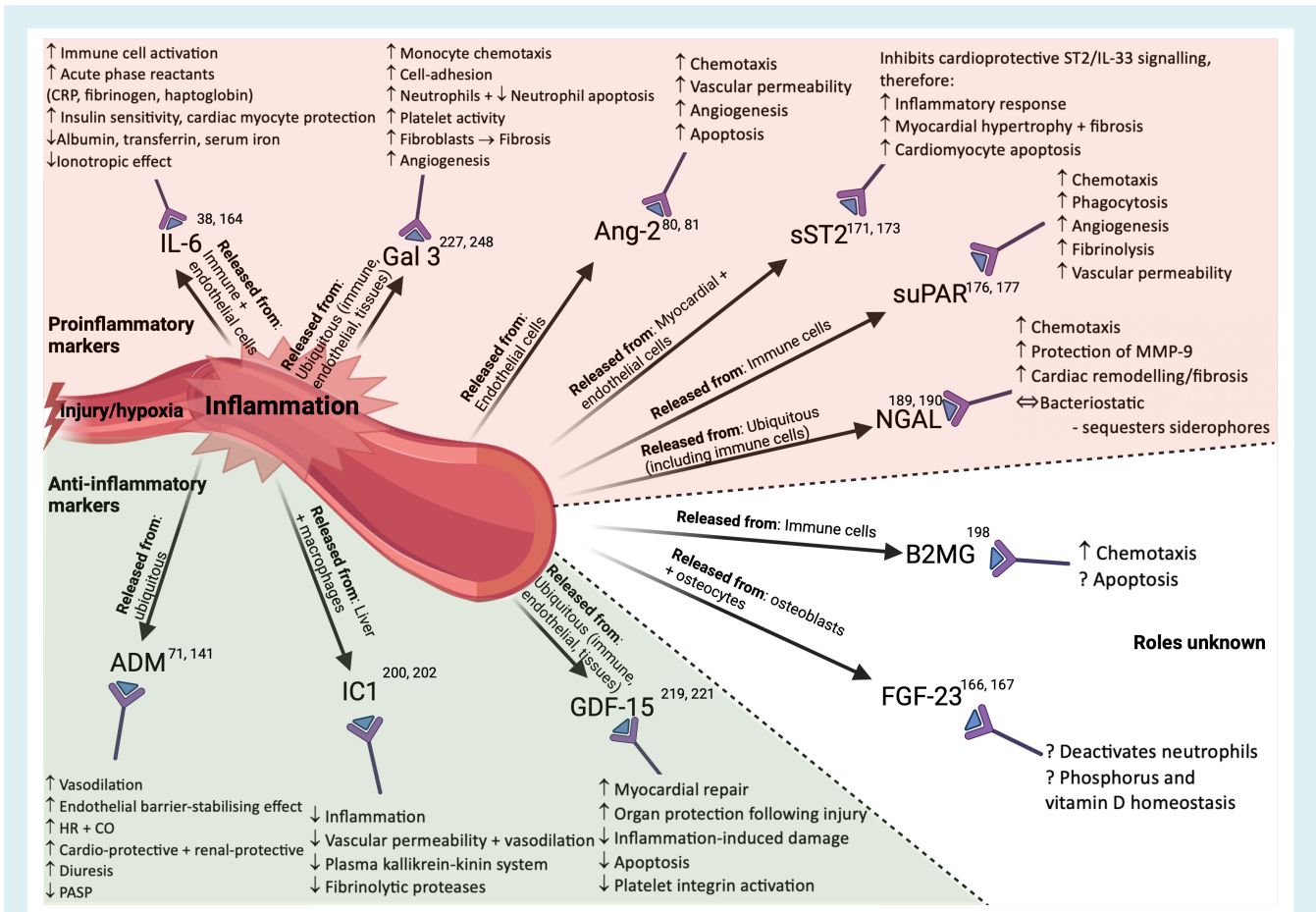


Figure 2 Summary of molecules released in response to inflammation in cardiogenic shock which act potentially in a proinflammatory and anti-inflammatory fashion. Injury and hypoxia lead to inflammation that results in the release of a variety of molecules. Traditionally these have been associated with worsening hypoperfusion, ischaemia and end-organ dysfunction. However, many molecules are likely to have differing effects depending on their target tissue and concentration, and while some are part of the immune system activation and lead to chemotaxis, fibrosis, and apoptosis, others act in a cardioprotective manner trying to promote healing, stabilization and limit inflammation. ADM, adrenomedullin; Ang-2, angiotensin-2; B2MG, beta-2 microglobulin; CO, cardiac output; CRP, C-reactive protein; FGF-23, fibroblast growth factor 23; Gal-3, galectin 3; GDF-15, growth differentiation factor 15; HR, heart rate; IC1, C1 inhibitor protein; IL-6, interleukin-6; IL-33, interleukin-33; MMP-9, matrix metalloproteinase-9; NGAL, plasma neutrophil gelatinase-associated lipocalin; NRI, net reclassification improvement; PASP, pulmonary artery systolic pressure; sST2, soluble suppressor of tumorigenicity 2; suPAR, soluble urokinase-type plasminogen activator receptor.

were associated with a roughly 10-fold increased 30-day mortality, and remained independently predictive after adjustment for established risk factors.⁸⁷ Thus, cDDP3 holds promise as a marker of both CS onset and severity, although validation of these early findings is required.

Novel biomarkers predicting mortality in cardiogenic shock

Markers of hypoperfusion

Intestinal fatty acid binding protein

Found in small bowel enterocytes, intestinal fatty acid binding protein (I-FABP) is released during intestinal hypoperfusion or

congestion.¹⁵⁵ In patients with CS or acute HF, elevated I-FABP levels on admission were associated with 30-day mortality.¹⁰¹ In acute HF, the addition of I-FABP to a prediction model for mortality that included age and NT-proBNP, significantly improved its accuracy.^{101,156} However, I-FABP is a non-specific marker elevated in all forms of shock, where it is also associated with 28-day mortality.¹⁵⁷

Markers of inflammation

Angiotensin-2

Angiotensin-2 (Ang-2) is released from endothelial cells in response to cytokines, which subsequently leads to impaired endothelial integrity. It is involved in the systemic inflammatory response and regulates vascular tone, as well as capillary

Table 2 Novel biomarkers studied in risk stratification of cardiogenic shock

Potential future biomarkers	Studies + (patient n=)	Aetiology of CS	Highest AUC for mortality (95% CI)	Investigated timing of biomarker	NRI available	External validation	Cardiac specific?	Goes up in sepsis?	Goes up in malignancy?	Predicts onset of CS	Predicts mortality
Individual markers											
Ang-2 ⁸⁰	Studies = 3 CS Patients = 323	ACS, HF	28-day mortality = 0.71 ⁸¹ 1-year mortality = 0.71 ⁸⁰	Day of admission to ICU Day of admission (within 12h of CS onset)	No	Yes	No	Yes ⁸²	Yes ⁸³	N/A	Yes
Co-peptin ⁸⁴	Studies = 1 CS Patients = 225	ACS	N/A	On admission to cath lab	No	No	No	Yes ⁸⁵	Unlikely ⁸⁵	Yes ⁸⁴	N/A
cDPP3 ⁸⁷	Studies = 3 CS Patients = 166	ACS, HF	90-day mortality = 0.60	At 'onset' of CS	No	Yes	No	Yes ⁸⁸	Yes ⁸⁹	Yes	Yes
Gal-3 ⁹⁰	Studies = 1 CS Patients = 40	ACS	30-day mortality = 0.70 (0.51–0.88)	At admission to hospital	No	No	No	Yes ⁹¹	Yes ⁹²	N/A	Yes
GDF-15 ⁹³	Studies = 2 CS Patients = 367	ACS	90-day mortality = 0.70 (0.62–0.77)	At 'onset' of CS	Yes	Yes	No	Yes ⁸⁴	Yes ⁹⁵	N/A	Yes
ADM ⁷¹	Studies = 3 CS Patients = 277	ACS, HF	90-day mortality = 0.81 (0.74–0.88) 30-day mortality = 0.71 (0.55–0.86) 90-day mortality = 0.80 (0.78–0.91)	At 12h following CS At 'inclusion' defined as CS At 5–10 days	No	Yes	No	Yes ⁹⁶	Yes ⁹⁷	Yes ⁸⁴	Yes
proANP ⁸⁴	Studies = 1 CS Patients = 225	ACS	N/A	On admission to cath lab	No	No	Yes	Yes ⁹⁸	N/A	Yes	N/A
sSTZ ⁸⁴	Studies = 5 CS Patients = 402	Mainly ACS; HF	30-day mortality = 0.55 30-day mortality = 0.93	At 'inclusion' defined as CS At 10 days	No	No	No	Yes ⁹⁹	Yes ¹⁰⁰	Yes ⁸⁴	Yes
I-FABP ¹⁰¹	Studies = 1 CS Patients = 90	ACS/HF	30-day mortality = 0.72 (0.62–0.82)	At admission to ICU	No	No	No	Yes ¹⁰²	No	N/A	Yes
suPAR ¹⁰³	Studies = 1 CS Patients = 161	ACS	90-day mortality = 0.72	At 'inclusion' with CS (within 6h of CS onset)	No	No	No	Yes ¹⁰⁴	Yes ¹⁰⁵	N/A	Yes
Cystatin C ¹³	Studies = 1 CS Patients = 190	ACS	1-year mortality = 0.57	At admission to hospital	No	No	No	No ⁹⁶	Yes ¹⁰⁷	N/A	Yes
KIM-1 ³³	Studies = 1 CS Patients = 190	ACS	1-year mortality = 0.60	At admission to hospital	No	No	No	Yes ¹⁰⁸	Yes ¹⁰⁹	N/A	Yes
P-NGAL ³³	Studies = 2 CS Patients = 344	Mainly ACS	90-day mortality = 0.78	At 24h	No	Yes	No	Yes ¹¹⁰	Yes ¹¹¹	N/A	Yes
IL-6 ³⁸	Studies = 2 CS Patients = 270	ACS	1-year mortality = 0.62 30-day mortality = 0.825	At admission to hospital At admission to hospital	No	Yes	No	Yes ¹¹²	Yes ¹¹³	N/A	Yes
FGF-23 ¹¹⁴	Studies = 1 CS Patients = 51	ACS	90-day mortality = 0.74 (0.66–0.82) 28-day mortality = 0.69	At 24h At admission to ICU	No	No	No	No ¹¹⁵	Yes ¹¹⁶	N/A	Yes
P-PENK ¹¹⁷	Studies = 1 CS patients = 154	ACS	90-day mortality = 0.68	At 'inclusion' with CS (within 6h of CS onset)	No	No	No	Yes ¹¹⁸	N/A	N/A	Yes
90-day mortality = 0.76				At 24h							
Combination scores											
CLIP (cystatin C, lactate, IL-6, and NT-proBNP) ¹¹⁹	Studies = 1 CS Patients = 458	ACS	30-day mortality = 0.83 (0.77–0.90)	On admission to cath lab	No	Yes	No	Yes	N/A	N/A	Yes
CS4P (L-FABP, B2MG, ALDOB, and ICI) ¹²⁰	Studies = 1 CS Patients = 48	ACS	90-day mortality = 0.83 (0.74–0.89)	Derivation: On admission – 24h Validation: within 6h of CS	Yes	Yes	No	N/A	N/A	N/A	Yes

Table 2 (Continued)

Potential future biomarkers	Correlates with end-organ dysfunction in CS							MCS		
	Brain	Heart	Lung	Renal	Liver	Intestine	Haematologic/ Bleeding	Predicts mortality on ECMO/MCS	Predicts weaning off ECMO	Predicts weaning off MCS
Individual markers										
Ang-2 ²⁰	N/A	Yes	N/A	Yes	N/A (potentially ¹²³)	N/A	Yes	Yes	N/A	N/A
Co-peptin ⁸⁴	N/A	Yes	N/A	N/A (potentially ¹²³)	N/A	N/A	N/A	N/A	Unlikely ³⁵	N/A
cDPP3 ³⁷	N/A	Yes	N/A	N/A (potentially ¹²³)	N/A	N/A	N/A	N/A	N/A	N/A
Gal-3 ³⁰	N/A	Yes	N/A (potentially ¹²⁴)	N/A (potentially ¹²⁴)	N/A (potentially ¹²⁴)	N/A (potentially ¹²⁴)	N/A (potentially ¹²⁴)	Yes	N/A (unlikely ¹²⁶)	N/A
GDF-15 ⁵³	N/A (potentially ¹²⁵)	Yes	N/A	N/A (potentially ¹²⁵)	N/A	N/A	N/A	N/A	N/A	N/A
ADM ⁷¹	N/A	Yes	N/A	N/A (potentially ¹²²)	N/A	N/A	N/A	N/A	Unlikely ³⁵	N/A
proANP ⁸⁴	N/A	Yes	N/A	N/A	N/A	N/A	N/A	N/A	Unlikely ³⁵	N/A
sST2 ⁸⁴	N/A	Yes	N/A	Yes	N/A (potentially ¹³³)	N/A	N/A	Yes	N/A (potentially ¹²⁶)	N/A
suPAR ¹⁰³	N/A	Yes	N/A	Yes	N/A (potentially ¹³³)	No (potentially ¹⁰⁵)	N/A	N/A	N/A	N/A
Cystatin C ²³	N/A (potentially ¹³⁴)	Yes	N/A	N/A (potentially ¹³⁵)	N/A (potentially ¹³⁴)	N/A	No ³⁷	N/A	N/A	N/A
KIM-1 ³³	N/A	N/A	N/A	Yes	N/A	N/A	N/A	N/A	N/A	N/A
P-NGAL ³³	N/A	Yes	N/A	Yes	N/A	N/A	N/A	N/A	N/A	N/A
IL-6 ³⁸	N/A	Yes	N/A	Yes	N/A	N/A	N/A	N/A	N/A	N/A
FGF-23 ¹¹⁴	N/A	Yes	N/A	Yes	N/A	N/A (potentially ¹³⁸)	N/A	Yes	N/A	N/A
P-PENK ¹¹⁷	N/A	Yes	N/A	N/A (potentially ¹³⁹)	N/A	N/A	N/A	N/A	N/A	N/A
Combination scores										
CLIP (cystatin C, lactate, IL-6, and NT-proBNP) ¹¹⁹	N/A	Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CS4P (L-FABP, B2MG, ALDOB, and IC1) ¹²⁰	N/A	Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

The table summarizes their predictive ability in CS, their correlation with end-organ dysfunction and whether their use has been studied in the context of MCS. As concurrent diseases, such as sepsis and malignancy, may confound the state of CS, it is important to consider whether the biomarkers change in response to these conditions and is included in the table.

The table is colour-coded according to whether this information is available: □ Yes; □ No; □ No evidence available.

ACS, acute coronary syndrome; ADM, adrenomedullin; ALDOB, aldolase B; Ang-2, angiotensin-2; AUC, area under the curve; B2MG, beta-2-microglobulin; cDPP3, circulating dipeptidyl peptidase 3; CI, confidence interval; CS, cardiogenic shock; CS4P, cardiogenic shock 4 proteins; ECMO, extracorporeal membrane oxygenation; FGF-23, fibroblast growth factor 23; Gal-3, galectin 3; GDF-15, growth differentiation factor 15; HF, heart failure; L-FABP, intestinal fatty acid binding protein; IC1, C1 inhibitor protein; IL-6, interleukin-6; KIM-1, kidney injury molecule-1; L-FABP, liver fatty acid binding protein; MCS, mechanical circulatory support; N/A, not available; NRI, net reclassification improvement; NT-proBNP, N-terminal pro-B-type natriuretic peptide; P-NGAL, plasma neutrophil gelatinase-associated lipocalin; P-PENK, plasma proenkephalin; proANP, pro-atrial natriuretic peptide; sST2, soluble suppressor of tumorigenicity 2; suPAR, soluble urokinase-type plasminogen activator receptor.

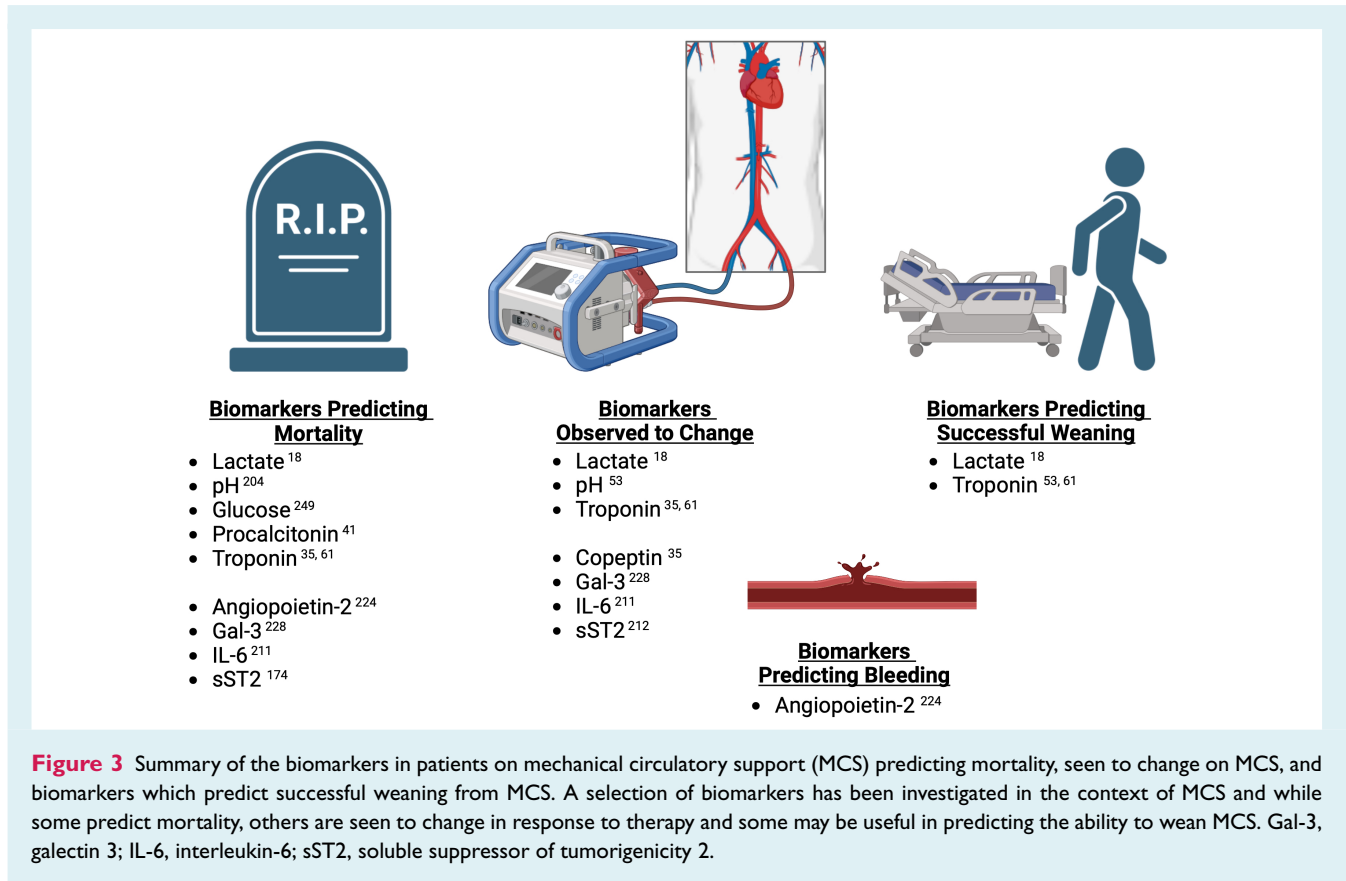


Figure 3 Summary of the biomarkers in patients on mechanical circulatory support (MCS) predicting mortality, seen to change on MCS, and biomarkers which predict successful weaning from MCS. A selection of biomarkers has been investigated in the context of MCS and while some predict mortality, others are seen to change in response to therapy and some may be useful in predicting the ability to wean MCS. Gal-3, galectin 3; IL-6, interleukin-6; sST2, soluble suppressor of tumorigenicity 2.

permeability.^{158,159} In sepsis, Ang-2 levels not only discriminate between sepsis and septic shock, but also correlate with mean arterial pressure, creatinine, PCT and the Sequential Organ Failure Assessment score.¹⁶⁰ In chronic HF patients, a stepwise increase in Ang-2 was observed with worsening New York Heart Association class, 6-min walk test and peak oxygen consumption, but did not correlate with LV function.¹⁶¹ Moreover, elevated Ang-2 levels are associated with increased cardiovascular mortality in the general population.¹⁶²

In the Intra-Aortic Balloon Pump (IABP)-SHOCK II trial, Ang-2 levels were predictive of 30-day and 1-year all-cause mortality, independent of IABP therapy.⁸⁰ The prognostic value of Ang-2 levels increased as levels rose from day 1 to day 3 in patients who died within 30 days of admission. Furthermore, Ang-2 levels correlated with cardiac power index, a strong predictor of mortality in CS.^{80,163}

Interleukin-6

Interleukin-6 is released during systemic inflammation and, besides its effect on vessels, has negative effects on the myocardium.¹⁶⁴ In a subanalysis of 183 patients in the CardShock study, IL-6 was found to be a reliable and early marker of 30-day all-cause mortality in ACS complicated by CS, with one of the highest AUCs among a range of biomarkers including NT-proBNP and PCT. While IL-6 is associated with clinical and biochemical signs of hypoperfusion, it lacks specificity for CS.^{38,39}

Fibroblast growth factor 23

Fibroblast growth factor 23 (FGF-23) was first discovered in osteoblasts and osteocytes and is involved in the regulation of phosphate levels.¹⁶⁵ Interestingly, FGF-23 is predictive of MACE in both CKD and elderly patients.^{166,167} *In vivo* and *in vitro* studies show adverse effects of FGF-23 on the myocardium, with elevated FGF-23 levels linked to adverse events in chronic HF.¹⁶⁸ In CS, a rise in FGF-23 levels is associated with increased 28-day mortality.¹¹⁴ However, whether elevation in FGF-23 levels reflects reduced filtration or excess myocardial production, remains unclear.^{169,170} Furthermore, whether FGF-23 plays an active role in this process or is simply a bystander marker, is also unclear.

Soluble suppressor of tumorigenicity 2

Suppressor of tumorigenicity 2 (ST2) is a member of the IL-1 receptor family. In inflammation, IL-33 signals via the ST2 pathway and provides myocardial protection.¹⁷¹ Soluble ST2 (sST2) acts as a decoy receptor blocking signalling and is associated with pro-fibrotic cardiac remodelling and adverse outcomes in chronic HF.¹⁷² sST2 is elevated on day 1 after acute myocardial infarction and is inversely correlated with LV systolic function.¹⁷³ Combining sST2 and NT-proBNP was predictive of 30-day all-cause mortality and improved the prediction of outcome when added to the CardShock score.¹⁷⁴ Small studies in CS found that prediction of mortality increases with time from onset of CS (Table 2). Together, sST2

and bicarbonate levels predicted the requirement for renal replacement therapy after initiation of extracorporeal membrane oxygenation (ECMO).¹⁷⁵ However, sST2 is not cardio-specific, with higher levels present in sepsis, compared to those in CS or STEMI.¹⁷⁶

Soluble urokinase-type plasminogen activator receptor

Soluble urokinase-type plasminogen activator receptor (suPAR) is a cleavage product of the urokinase-type plasminogen activator receptor (uPAR) that is involved in inflammation, fibrinolysis, apoptosis, tissue remodelling, cell adhesion and migration, and may play a part in the formation of metastases.^{177,178} Once cleaved into suPAR, it remains stable and is actively involved in inflammatory chemotaxis.¹⁷⁹ Levels increase as part of systemic inflammation, in infection, cancer and cardiovascular disease, and are associated with increased mortality.^{104,180}

In a subset of 161 patients from the CardShock study, mainly with ACS, suPAR was independently predictive of a nearly six-fold increase in 90-day all-cause mortality, with the addition of 12-h suPAR levels to the CardShock risk score significantly improving mortality prediction.¹⁰³ SuPAR levels in CS are lower than in sepsis, indicating a potential use for this marker in differentiating these two conditions. SuPAR levels correlated with markers of end-organ dysfunction such as creatinine, eGFR, NT-proBNP and CRP.¹⁰³

Predictors of acute kidney injury

As the number of organs affected by CS increases, the mortality rate also increases.^{68,181} Hypoperfusion and/or congestion lead to progressive multi-organ failure, as reflected by a rise in biomarkers of renal and liver dysfunction. Approximately a third of patients with CS develop acute kidney injury (AKI), which is associated with a poor prognosis.⁶⁸ The most frequently used marker of AKI is creatinine, which is utilized in risk assessment systems such as the IABP-SHOCK II score.^{20,182} More sensitive markers of AKI such as Ang-2, cystatin C, kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL) and proenkephalin (PENK), have been evaluated in CS (see below). However, their prognostic utility has shown conflicting results across the studies.^{117,183}

Angiotensin-2

In the IABP-SHOCK II substudy, Ang-2 measured on admission was an independent predictor of AKI in patients with CS. However, Ang-2 levels were not associated with cystatin C levels, suggesting that Ang-2 elevation does not relate to reduced renal clearance.⁸⁰

Kidney injury molecule-1

Kidney injury molecule-1 is a transmembrane glycoprotein expressed in kidneys and other organs. It is upregulated in the proximal renal tubules during ischaemia-reperfusion injury.^{184,185} A meta-analysis demonstrated that urinary KIM-1 exhibits good sensitivity and specificity for the prediction of AKI,¹⁸⁶ especially following cardiopulmonary bypass.¹⁸⁷ Although KIM-1 was shown to be highly predictive of long-term decline in renal function in healthy individuals, in the setting of CS, it does not offer additional prognostic information beyond creatinine alone.^{33,188}

Neutrophil gelatinase-associated lipocalin

Neutrophil gelatinase-associated lipocalin is a molecule secreted by neutrophils and renal tubular epithelial cells. It is one of the earlier markers of AKI, with plasma levels rising within 2 to 6 h after renal insult.^{189,190} Collectively, the evidence regarding the predictive utility of markers such as cystatin C and NGAL in ACS and CS is conflicting.^{117,183}

Proenkephalin

Proenkephalin is a stable marker of the endogenous opioid system that has cardio-depressive effects.¹⁹¹ High levels correlate with advanced HF, deteriorating renal function and mortality.¹⁹¹ PENK levels correlate well with eGFR and unlike NGAL, are not influenced by inflammation and predict the need for renal replacement therapy in sepsis.^{192,193} In CS, both NGAL and PENK were independently associated with AKI and strongly predictive of 90-day mortality.¹¹⁷

Combining biomarkers in cardiogenic shock

In a study of 2002 patients with STEMI, 225 of whom developed CS, four proteins were identified as early, independent predictors of CS. These included copeptin, MR-proADM, pro-atrial natriuretic peptide and sST2, and as their individual levels increased, so did the risk of CS.⁸⁴ The addition of all four markers to the ORBI score significantly improved the prediction of evolving CS, with an AUC of 0.85.

Cardiogenic shock 4 proteins

A recent quantitative study identified 51 proteins that are elevated in CS following STEMI, among which the four best predictors of 90-day all-cause mortality were liver-type fatty acid-binding protein (L-FABP), beta-2-microglobulin (B2MG), fructose-bisphosphate aldolase B (ALDOB), and SerpinG1 (IC1). These four proteins were thus termed 'cardiogenic shock 4 proteins' (CS4P).¹²⁰ CS4P was validated in the CardShock cohort, and found to be predictive of 90-day all-cause mortality with an AUC of 0.83.²¹ Using the CS4P with the CardShock risk score showed a marked benefit in patient reclassification over the CardShock score alone, with a NRI of 0.49 ($p=0.02$). Using the CS4P with the IABP-SHOCK II risk score also showed a marked benefit in patient reclassification over the IABP-SHOCK II risk score alone, with a NRI of 0.57 ($p=0.032$).¹²⁰ The success of these four proteins may lie in the combination of organ systems that they represent.¹²⁰

Liver dysfunction is associated with increased all-cause mortality.¹⁸¹ L-FABP, a soluble protein found in hepatocytes and, to a lesser extent, in kidneys, intestine and lung,^{194,195} plays a protective role, binding and controlling potentially cytotoxic metabolites.¹⁹⁶ It is upregulated in response to tissue injury and is not CS-specific.¹²⁰ When measured within 24 h of CS admission, L-FABP substantially improves the prediction of death, over clinical risk scores.¹²⁰ ALDOB is another marker of liver damage.¹²⁰

Beta-2-microglobulin, elevated in coronary artery disease, is a marker of future MACE, but has not been evaluated specifically in CS.¹⁹⁸ Levels increase in response to kidney injury, which in turn is associated with increased CS mortality.^{68,199}

Increased levels of IC1, part of the complement pathway of inflammation,²⁰⁰ correlate with increased 30-day mortality in patients with CS,²⁰¹ while inhibition of IC1 in STEMI patients may provide myocardial protection from reperfusion injury.²⁰²

Cystatin C, lactate, interleukin-6 and NT-proBNP

In patients with CS due to STEMI who were recruited to the Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial,²⁰³ integration of four out of 58 investigated proteins into a clinical risk model (CLIP score) allowed for highly accurate prediction of 30-day all-cause mortality with an AUC of 0.83, a finding which the authors subsequently validated in the IABP-SHOCK II cohort.¹¹⁹ These proteins were cystatin C, lactate, IL-6 and NT-proBNP. The CLIP score outperformed the IABP-SHOCK II score in predicting 30-day mortality.

This four-component risk score incorporates cystatin C, which appears to be superior to creatinine in predicting AKI and mortality in ACS, HF, and during critical illness.^{204–206} Given its relatively short half-life, cystatin C levels change earlier than creatinine, providing a theoretical basis for its superiority as a marker. Furthermore, cystatin C was an independent predictor of MACE in patients with ACS, even without AKI, an effect likely mediated through its relationship with inflammation and atherosclerosis.^{207–209} However, in the IABP-SHOCK II trial, creatinine predicted mortality more reliably than cystatin C, NGAL, KIM-1, or eGFR.³³ There is no consensus on which marker is best.

A recent study comparing the performance of the CLIP score in CS, septic shock, haemorrhagic shock, respiratory failure and all intensive care admissions, found that the score predicted 30-day all-cause mortality similarly well in all these settings.²¹⁰

Importance of biomarker dynamics

Temporal changes in biomarker levels can improve risk assessment. Amongst patients with elevated cDPP3, those in whom cDPP3 levels had decreased at 24 h showed a lower risk of refractory CS and death compared to those with persistently elevated cDPP3 level.¹⁵¹ Likewise, ADM and lactate normalized in surviving patients, while persistent elevations were predictive of adverse outcome. Interestingly, the prognostic usefulness of lactate to predict mortality decreased from baseline (0 h) to 5–10 days, while that of ADM increased over the same period of time.⁷¹

In patients with CS, IL-6 is the predominant cytokine present in plasma. Following initiation of MCS, levels of IL-6 declined in survivors, but continued to rise in non-survivors.²¹¹ Similar trends were seen with sST2 in patients receiving LVAD support for end-stage CS. In a small study with serial sST2 measurements, sST2 levels were elevated just before LVAD implantation and decreased

substantially during MCS support, normalizing by 6 months.²¹² Another very small study showed that persistent elevation of sST2 following LVAD implantation was associated with higher 1-year mortality.²¹³

Use of biomarkers to predict complications on mechanical circulatory support

A major limitation of MCS is the high rate of vascular and bleeding complications. In a meta-analysis of 1866 patients on ECMO, major or significant bleeding occurred in 41%, lower limb ischaemia in 17% and stroke in 6%.²¹⁴ While patients on microaxial LVAD support also experience high complication rates, these are lower than with ECMO.²¹⁵

As blood flows through the tubing of MCS, the contact pathway of coagulation is activated, and coupled with inflammation, significantly increases the risk of thrombosis, necessitating anticoagulation.²¹⁶ Additionally, MCS exposes blood to high shear stress, resulting in conformational change in von Willebrand factor. This leads to cleavage of high molecular weight multimers into smaller complexes with reduced haemostatic potential, resulting in acquired von Willebrand syndrome.^{217,218} There are no formal guidelines on the optimal assessment of anticoagulation in patients on MCS, though some frameworks have been proposed.²¹⁶

Several markers have been evaluated as predictors of bleeding in CS patients. Growth differentiation factor 15 (GDF-15) is a transforming growth factor- β that is upregulated in a number of conditions including cardiovascular disease. Levels are thought to rise as a consequence of tissue ischaemia and inflammation.²¹⁹ In animals, GDF-15 inhibits platelet integrin activation, prevents thrombosis and may serve as a marker of bleeding.^{220,221} In patients with coronary artery disease, GDF-15 predicts bleeding risk in a dose-dependent manner, including on antiplatelet agents and anticoagulation.^{131,220,222} In a prospective study of patients with CS attributable to ACS who were randomized to treatment with or without IABP as a pre-specified substudy of the IABP-SHOCK II trial, elevated GDF-15 levels during percutaneous coronary intervention were predictive of 30-day all-cause mortality, even after adjusting for other known predictors such as lactate.⁹³ Adding GDF-15 to the CardShock risk score improved the risk stratification of CS (NRI 0.18, $p=0.003$).²²³ However, there is a lack of data supporting the use of GDF-15 as a marker of bleeding risk during MCS.

The inflammatory cytokine Ang-2, stored in the Weibel–Palade bodies of endothelial cells, is released in response to stimuli such as thrombin and hypoxia.¹⁵⁹ In patients with CS, baseline Ang-2 levels were not predictive of 30-day mortality, but levels were generally observed to decline following the initiation of MCS. Furthermore, persistently elevated levels were predictive of adverse outcomes.²²⁴ In patients with acute myocardial infarction complicated by CS, Ang-2 levels were associated with the development of AKI, bleeding complications, and/or the need for blood transfusion, and unaffected by IABP support.⁸⁰ In other settings, however,

Ang-2 levels have been related to the occurrence of thrombotic events.^{225,226}

Galectin 3 (Gal-3) is a galactoside-binding protein involved in cell–cell and cell–matrix interactions, and implicated in atherosclerosis, myocardial fibrosis and HF. In a small study of patients with ACS-related CS, low Gal-3 levels were associated with increased 30-day mortality.⁹⁰ In a murine model, Gal-3 was a marker of platelet hyperactivity and thrombus formation, and Gal-3 inhibition achieved a potent antithrombotic effect without excessive bleeding.²²⁷ In patients with severe chronic HF, Gal-3 levels fell after LVAD implantation or heart transplantation, and persistently elevated levels were associated with increased mortality.²²⁸

In summary, while biomarkers are predictive of adverse outcomes in patients on MCS, specific markers of excess bleeding and thrombosis risk in CS patients are lacking.

Biomarkers as treatment targets in cardiogenic shock

Several monoclonal antibodies are being explored for immunomodulatory treatment of septic shock.²²⁹ As a systemic inflammatory response is involved in both septic shock and CS, there may be some treatments that benefit both conditions.

Tocilizumab is an IL-6 targeting monoclonal antibody used in the treatment of rheumatoid arthritis and, more recently, severe acute respiratory syndrome coronavirus 2 infection.²³⁰ In patients presenting with out-of-hospital cardiac arrest (33% as a consequence of STEMI), treatment with tocilizumab resulted in a reduction of systemic inflammation and a rapid fall in myocardial injury markers in a third of patients at 6–12 h.²³¹ Its efficacy in preventing CS is currently being evaluated in patients with ACS at high risk of CS, in the ongoing double-blind, randomized controlled DOBERMANN trial.²³²

Complement activation plays an important role in the pathophysiology of shock and systemic inflammation. C1 esterase regulates the complement pathway, plasma kallikrein-kinin and coagulation systems, and elevated levels of C1-esterase are associated with poor prognosis in CS.¹²⁰ In a small, randomized, double-blind trial in which 80 patients with STEMI undergoing emergency coronary artery bypass grafting were randomized to a C1-esterase inhibitor or placebo, complement pathway inhibition was associated with shorter intubation time, shorter hospital stay, and reduced need for inotropic support.²⁰² However, another small study showed no effect of C1 esterase inhibition on mortality in patients undergoing emergency coronary artery bypass grafting for ACS.²³³ Notably however, C1 esterase inhibition was associated with reduced troponin levels.²³³

Circulating DPP3 is not only a useful biomarker in CS, but is also involved in myocardial depression. In mice, intravenous infusion of DPP3 immediately resulted in reduced myocardial contractility and impaired renal perfusion.²³⁴ While procizumab, a cDPP3-antibody, almost completely normalized cardiac function and renal perfusion in a murine model of isoproterenol-induced HF, it has not yet been tested in humans.²³⁴

Limitations of current data

Research into the pathophysiology, risk stratification and management of CS faces several challenges. Firstly, heterogeneity in the definition of CS is a significant limitation. Most trials and guidelines define CS as a systolic blood pressure (SBP) ≤ 90 mmHg for >30 min or the need for vasopressors/inotropes to maintain SBP >90 mmHg.²³⁵ However, CS can also present with normotension, with a similar poor prognosis to hypotensive CS. Unfortunately, the former group is usually excluded from trials.^{236,237} Recently, a consensus document from the Shock Academic Research Consortium aimed to standardize definitions and research into CS, although multiple, frequent changes in definition may lead to confusion.²³⁸

Secondly, CS is a condition with diverse aetiologies, including ischaemia, primary pump failure, valvular disease, arrhythmias or following bypass surgery. While some trials focused on a single aetiology of CS (predominantly ACS), many have grouped various aetiologies together. Although similar vicious cycles of maladaptive responses lead to further deterioration in cardiac output and ischaemia, differing pathophysiological causes may likely require different treatments, with variable response rates.

A significant limitation of most biomarkers is that they are non-specific, and seem to identify a ‘sick’ patient with high mortality, rather than a specific CS cohort, with specific risks. Accordingly, the elevation of circulating levels of most biomarkers in CS is considered to be an epiphenomenon and not pathologically causal. Some molecules (e.g. cDPP3 and IL-6) may represent potential biotargets to modulate cardiovascular outcomes.

The effect of distinct treatment decisions based on biomarkers, such as mechanical offloading, inotropic requirements or haemofiltration, has not been well characterized thus far. Furthermore, most of the available data on biomarkers in CS stem from a number of small studies and a few larger interventional trials. The larger studies were designed to assess the effect of interventions such as IABP in CS, and not specifically to examine biomarkers. Six biomarkers (see *Table 2*) and two scores (CS4P and CLIP score) have undergone some external validation for the prediction of mortality. These are often in heterogeneous populations using different cut-off values compared to those in the derivation cohorts. Further, more rigorous external validation is needed before these are integrated into protocols and used in clinical practice.

Furthermore, the findings from these studies are still limited to the populations in which they were conducted. There were no differences in sST2 levels between men and women with CS receiving LVAD support, while none of the other studies reported gender differences specifically.²¹² Local demographics, ethnicity, and clinical practices may influence the usefulness of the biomarkers and require further validation. Additionally, patients from specific demographics or with certain beliefs may have been excluded from these studies, further limiting the generalizability of the biomarkers.

Most of the novel biomarkers discussed herein are not widely available, require testing in specialized laboratories, and even then, the results are not available in a timely manner. CS is a time-critical condition, meaning that many of these markers are impractical for

Table 3 Ongoing observational and interventional trials investigating the levels of biomarkers in patients with cardiogenic shock

Name of trial	NCT	Patient population	Country	Start-end date
Cardiogenic Shock Integrated PHenotyping for Event Reduction (CIPHER)	NCT04323371	Patients with acute decompensated heart failure, complicated by CS	Italy	2020–2025
ECMOsorb Trial - Impact of a VA-ECMO in Combination With CytoSorb in Critically Ill Patients With Cardiogenic Shock (ECMOsorb)	NCT05027529	CS of any cause and indication for VA-ECMO	Germany	2021–2024
Normoxemic Versus Hyperoxemic Extracorporeal Oxygenation in Patients Supported by Veino-arterial ECMO for Cardiogenic Shock (ECMOxy)	NCT04990349	Patient supported by VA-ECMO for CS	France	2022–2024
Genomic Determinants of Outcome in Cardiogenic Shock (Goldilocks)	NCT05728359	CS secondary to AMI or myocarditis	UK	2022–2025
Role of Candidate Proteins in Capillary Leakage During Acute Circulatory Failure	NCT05586282	Circulatory shocks (including septic shock and CS)	France	2022–2026
Influence of Enteral Microbiome on Mortality of Patients With Cardiogenic Shock	NCT06006754	CS of all aetiology	Germany	2023–2024
PRrecision Ecmo in Cardlogenic Shock Evaluation (PRECISE)	NCT05748860	Patients who will be commenced on VA-ECMO (for CS or ECPR)	Australia and New Zealand	2023–2026

AMI, acute myocardial infarction; CS, cardiogenic shock; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

practical clinical use. Biomarkers that can be tested at the bedside would facilitate the rapid decision-making required in CS patients.

Cost-effectiveness is another crucial consideration when choosing tests for patients with CS. The usefulness of biomarkers will be determined not only by their sensitivity and specificity for predicting outcomes, but also by their added value (net reclassification) compared to current biomarkers and risk scores, taking into account the frequency of measurements and the availability of tests (including turnaround times/near-patient options) compared to more readily available biomarkers such as creatinine and lactate. Furthermore, determining the optimal timing and frequency of measurements to best guide prognosis and cost-effectiveness requires further study for all biomarkers.

These limitations indicate that we have not yet reached the point of establishing thresholds and timings that would allow for the incorporation of these new biomarkers into clinical use. Further research is therefore needed before any of the novel markers can be incorporated into routine use to help predict the onset of or the outcome of CS.

Future directions

Given the high mortality and morbidity of CS and the failure of many new treatment strategies, there is a significant need to improve outcomes. Important first steps are to standardize the definition of CS used in studies, to define the underlying aetiology leading to CS, as well as the shock stage at which a potential marker

is assessed. Indeed, many interventions may be effective in early (i.e. SCAI stages A-C), but not in fully developed CS (i.e. SCAI stages D-E).

Some novel biomarkers may have the potential to predict the onset of CS before it progresses to more severe stages. Identifying this risk early can facilitate prompt intervention, such as more invasive haemodynamic monitoring, and enable the use of early, targeted treatments. It also allows for thorough assessment and planning of escalation strategies.

New biomarkers that detect early end-organ hypoperfusion, before routinely available blood markers indicate organ damage, could help guide interventions to optimize haemodynamic support or escalate to MCS early. Bleeding and thrombotic complications are common in CS, especially in patients on MCS. Biomarkers could also help guide anticoagulation levels and predict thrombotic or bleeding events. Minimizing these complications may improve survival, particularly in patients on MCS.

However, to use the biomarkers for decision-making, we first need large prospective studies to evaluate biomarker trends in CS. Furthermore, research will be needed to transition the biomarker use from bench to bedside, to guide interventions and to determine whether these changes have meaningful effects on clinical outcomes.

Most studies have focused on relatively short-term outcomes (see Table 2). Patients discharged from the hospital often suffer from significant morbidity and remain at increased mortality risk, which can lead to rehospitalization.⁶ Biomarkers that predict

morbidity and readmission could be useful for enabling closer follow-up of patients post-discharge, to achieve the best long-term outcomes, whether that is active treatment or discussions around best supportive management.

Several studies, both observational and interventional, are in progress or planned, to evaluate existing and identify new biomarkers (Table 3). The ideal biomarker should be readily available for widespread use, ideally at the point-of-care, and give results in a suitably rapid manner to influence care. New combinations of biomarkers need to be examined to determine whether they perform better than individual markers alone.

Some biomarkers represent promising therapeutic targets. Many trials are currently searching for new targets in CS (Table 3). Multiple cytokines are generated during CS, and one strategy being explored involves removing these from the circulation using filtration with ECMO, although some cytokines may have protective functions in CS (Figure 2).²³⁹ Treatments targeting biomarkers at earlier stages of CS or pre-shock, are needed to define the 'sweet spot' for personalized therapeutic interventions. Future clinical trials should also explore a biomarker-tailored treatment approach. For example, patients with high levels of IL-6 may be prone to a mixed distributive-inflammatory phenotype of CS, which could respond to an anti-inflammatory treatment. In this regard, treatment of CS with the anti-IL-6 monoclonal antibody tocilizumab or the cDPP3 inhibitor procizumab, appear particularly promising.

Beyond proteomics

Working out the molecular signature of CS is not limited to focusing on proteomics.^{79,240} Since activation of transcription precedes protein formation, genomics and transcriptomics may also play an important role. This approach could allow the early detection of pathological processes, such as signatures of inflammation or AKI, enabling early implementation of treatment.²⁴¹ Upregulation of certain RNAs is associated with renal and brain protection from hypoxia which may be another potential therapeutic avenue to explore.^{242,243} Additionally, it could provide insights into genetic susceptibility, including to developing complications, with implications for management.²⁴⁴

Furthermore, with the rise of ultra-rapid genome sequencing, genomics may play a role in facilitating targeted treatments.²⁴⁵ In the future, artificial intelligence may be able to integrate multiple variables and assist with the personalization of treatment in CS.²⁴⁶

Conclusion

A number of novel biomarkers enhance mortality prediction in CS compared to conventional markers such as lactate, with some, such as ADM and cDPP3 able even to predict the development of CS. Temporal changes in biomarkers may guide prognostication particularly well. Many biomarkers reflect end-organ hypoperfusion or systemic inflammation, and are therefore not specific to CS. While some constitute potential therapeutic targets, the limitations of current biomarkers include lack of widespread availability, slow turnaround times, lack of specificity and limited prospective

validation. This highlights the significant unmet need in CS and provides clinicians with an overview of current and novel biomarkers, thereby stimulating future research into and validation of these biomarkers. Future studies assessing novel biomarkers to predict the onset and prognosis in CS, assess the impact of interventions and act as therapeutic targets could enhance the outcome in this very high-risk cohort.

Conflict of interest: F.A.W. has received support from the Foundation for Cardiovascular Research – Zurich Heart House, the Theodor und Ida Herzog-Egli Foundation, the Lindenhof Foundation, the European Society of Cardiology, the Swiss Heart Foundation, the Fonds zur Förderung des akademischen Nachwuchses of the University of Zurich, the Medical University of Graz, the Sphingotec GmbH, the 4TEEN4 Pharmaceuticals GmbH, and the PAM Theragnostics GmbH outside this work. V.P. has received consulting fees from Johnson & Johnson and Abiomed. D.A.G. has received institutional research grants from Bayer, AstraZeneca, Werfen and Medtronic, and advisory board/steering committee roles with BMS, Janssen and Chiesi. All other authors have nothing to disclose.

References

- Chioncel O, Parissis J, Mebazaa A, Thiele H, Desch S, Bauersachs J, et al. Epidemiology, pathophysiology and contemporary management of cardiogenic shock – A position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:1315–1341. <https://doi.org/10.1002/ehf.1922>
- Naidu SS, Baran DA, Jentzer JC, Hollenberg SM, Van Diepen S, Basir MB, et al. SCAI SHOCK stage classification expert consensus update: A review and incorporation of validation studies. *J Am Coll Cardiol* 2022;**79**:933–946. <https://doi.org/10.1016/j.jacc.2022.01.018>
- Tehrani BN, Truesdell AG, Psotka MA, Rosner C, Singh R, Sinha SS, et al. A standardized and comprehensive approach to the management of cardiogenic shock. *JACC Heart Fail* 2020;**8**:879–891. <https://doi.org/10.1016/j.jchf.2020.09.005>
- Hunziker L, Radovanovic D, Jeger R, Pedrazzini G, Cuculi F, Urban P, et al.; AMIS Plus Registry Investigators. Twenty-year trends in the incidence and outcome of cardiogenic shock in AMIS Plus Registry. *Circ Cardiovasc Interv* 2019;**12**:e007293. <https://doi.org/10.1161/CIRCINTERVENTIONS.118.007293>
- Lang CN, Kaier K, Zotzmann V, Stachon P, Pottgiesser T, Von Zur MC, et al. Cardiogenic shock: Incidence, survival and mechanical circulatory support usage 2007–2017 – insights from a national registry. *Clin Res Cardiol* 2021;**110**:1421–1430. <https://doi.org/10.1007/s00392-020-01781-z>
- Sterling LH, Fernando SM, Talarico R, Qureshi D, Van Diepen S, Herridge MS, et al. Long-term outcomes of cardiogenic shock complicating myocardial infarction. *J Am Coll Cardiol* 2023;**82**:985–995. <https://doi.org/10.1016/j.jacc.2023.06.026>
- Shankar A, Gurumurthy G, Sridharan L, Gupta D, Nicholson WJ, Jaber WA, et al. A clinical update on vasoactive medication in the management of cardiogenic shock. *Clin Med Insights Cardiol* 2022;**16**:11795468221075064. <https://doi.org/10.1177/11795468221075064>
- Yu X, Ge L, Niu L, Lian X, Ma H, Pang L. The dual role of inducible nitric oxide synthase in myocardial ischemia/reperfusion injury: Friend or foe? *Oxid Med Cell Longev* 2018;**2018**:8364848. <https://doi.org/10.1155/2018/8364848>
- Hochman JS. Cardiogenic shock complicating acute myocardial infarction: Expanding the paradigm. *Circulation* 2003;**107**:2998–3002. <https://doi.org/10.1161/01.CIR.0000075927.67673.F2>
- Lassus J, Tarvasmäki T, Tolppanen H. Biomarkers in cardiogenic shock. *Advances in clinical chemistry*. Amsterdam: Elsevier; 2022. p31–73. <https://doi.org/10.1016/bs.acc.2022.03.002>
- Krychtiuk KA, Vrints C, Wojta J, Huber K, Speidl WS. Basic mechanisms in cardiogenic shock: Part 2 – Biomarkers and treatment options. *Eur Heart J Acute Cardiovasc Care* 2022;**11**:366–374. <https://doi.org/10.1093/ehjacc/zuac022>
- Iborra-Egea O, Montero S, Bayes-Genis A. An outlook on biomarkers in cardiogenic shock. *Curr Opin Crit Care* 2020;**26**:392–397. <https://doi.org/10.1097/MCC.0000000000000739>
- Wang J, Shen B, Feng X, Zhang Z, Liu J, Wang Y. A review of prognosis model associated with cardiogenic shock after acute myocardial infarction. *Front Cardiovasc Med* 2021;**8**:754303. <https://doi.org/10.3389/fcvm.2021.754303>

14. Kalra S, Ranard LS, Memon S, Rao P, Garan AR, Masoumi A, et al. Risk prediction in cardiogenic shock: Current state of knowledge, challenges and opportunities. *J Card Fail* 2021;**27**:1099–1110. <https://doi.org/10.1016/j.cardfail.2021.08.003>
15. Jentzer JC, Schrage B, Patel PC, Kashani KB, Barsness GW, Holmes DR, et al. Association between the acidemia, lactic acidosis, and shock severity with outcomes in patients with cardiogenic shock. *J Am Heart Assoc* 2022;**11**:e024932. <https://doi.org/10.1161/JAHA.121.024932>
16. Chang Y, Antonescu C, Ravindranath S, Dong J, Lu M, Vicario F, et al. Early prediction of cardiogenic shock using machine learning. *Front Cardiovasc Med* 2022;**9**:862424. <https://doi.org/10.3389/fcvm.2022.862424>
17. Marbach JA, Di Santo P, Kapur NK, Thayer KL, Simard T, Jung RG, et al. Lactate clearance as a surrogate for mortality in cardiogenic shock: Insights from the DOREMI trial. *J Am Heart Assoc* 2022;**11**:e023322. <https://doi.org/10.1161/JAHA.121.023322>
18. Scolari FL, Schneider D, Fogazzi DV, Gus M, Rover MM, Bonatto MG, et al. Association between serum lactate levels and mortality in patients with cardiogenic shock receiving mechanical circulatory support: A multicenter retrospective cohort study. *BMC Cardiovasc Disord* 2020;**20**:496. <https://doi.org/10.1186/s12872-020-01785-7>
19. Fuernau G, Desch S, De Waha-Thiele S, Eitel I, Neumann FJ, Hennersdorf M, et al. Arterial lactate in cardiogenic shock: Prognostic value of clearance versus single values. *JACC Cardiovasc Interv* 2020;**13**:2208–2216. <https://doi.org/10.1016/j.jcin.2020.06.037>
20. Pöss J, Köster J, Fuernau G, Eitel I, De Waha S, Ouarrak T, et al. Risk stratification for patients in cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol* 2017;**69**:1913–1920. <https://doi.org/10.1016/j.jacc.2017.02.027>
21. Harjola V, Lassus J, Sionis A, Køber L, Tarvasmäki T, Spinar J, et al. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. *Eur J Heart Fail* 2015;**17**:501–509. <https://doi.org/10.1002/ejhf.260>
22. Ostenfeld S, Lindholm MG, Kjaergaard J, Bro-Jeppesen J, Møller JE, Wanscher M, et al. Prognostic implication of out-of-hospital cardiac arrest in patients with cardiogenic shock and acute myocardial infarction. *Resuscitation* 2015;**87**:57–62. <https://doi.org/10.1016/j.resuscitation.2014.11.010>
23. Cheng JM, Helming AM, van Vark LC, Kardys I, Den Uil CA, Jewbali LSD, et al. A simple risk chart for initial risk assessment of 30-day mortality in patients with cardiogenic shock from ST-elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2016;**5**:101–107. <https://doi.org/10.1177/2048872615568966>
24. Frydland M, Møller JE, Wiberg S, Lindholm MG, Hansen R, Henriques JPS, et al. Lactate is a prognostic factor in patients admitted with suspected ST-elevation myocardial infarction. *Shock* 2019;**51**:321–327. <https://doi.org/10.1097/SHK.0000000000001191>
25. Rusnak J, Schupp T, Weidner K, Ruka M, Egner-Walter S, Forner J, et al. Impact of lactate on 30-day all-cause mortality in patients with and without out-of-hospital cardiac arrest due to cardiogenic shock. *J Clin Med* 2022;**11**:7295. <https://doi.org/10.3390/jcm11247295>
26. Martínez-Solano J, Sousa-Casasnovas I, Bellón-Cano JM, García-Carreño J, Juárez-Fernández M, Díez-Delgado F, et al. Lactate levels as a prognostic predictor in cardiogenic shock under venoarterial extracorporeal membrane oxygenation support. *Rev Esp Cardiol (Engl Ed)* 2022;**75**:595–603. <https://doi.org/10.1016/j.rec.2021.08.020>
27. Mariappan R, Venkatraghavan L, Vertanian A, Agnihotri S, Cynthia S, Reyhani S, et al. Serum lactate as a potential biomarker of malignancy in primary adult brain tumours. *J Clin Neurosci* 2015;**22**:144–148. <https://doi.org/10.1016/j.jocn.2014.06.005>
28. Yang J, Song P, Song Y, Hahn JY, Choi SH, Choi JH, et al. Prognostic value of admission blood glucose level in patients with and without diabetes mellitus who sustain ST segment elevation myocardial infarction complicated by cardiogenic shock. *Crit Care* 2013;**17**:R218. <https://doi.org/10.1186/cc13035>
29. Choi SH, Yoon GS, Lee MJ, Park SD, Ko YG, Ahn CM, et al. Prognostic impact of plasma glucose on patients with cardiogenic shock with or without diabetes mellitus from the SMART RESCUE trial. *Am J Cardiol* 2022;**175**:145–151. <https://doi.org/10.1016/j.amjcard.2022.04.008>
30. Zeller M, Cottin Y, Brindisi MC, Dentan G, Laurent Y, Janin-Manificat L, et al. RICO Survey Working Group. Impaired fasting glucose and cardiogenic shock in patients with acute myocardial infarction. *Eur Heart J* 2004;**25**:308–312. <https://doi.org/10.1016/j.ehj.2003.12.014>
31. Vis MM, Sjauw KD, van der Schaaf RJ, Baan J, Koch KT, DeVries JH, et al. In patients with ST-segment elevation myocardial infarction with cardiogenic shock treated with percutaneous coronary intervention, admission glucose level is a strong independent predictor for 1-year mortality in patients without a prior diagnosis of diabetes. *Am Heart J* 2007;**154**:1184–1190. <https://doi.org/10.1016/j.ahj.2007.07.028>
32. Kataja A, Tarvasmäki T, Lassus J, Cardoso J, Mebazaa A, Køber L, et al. The association of admission blood glucose level with the clinical picture and prognosis in cardiogenic shock – results from the CardShock study. *Int J Cardiol* 2017;**226**:48–52. <https://doi.org/10.1016/j.ijcard.2016.10.033>
33. Fuernau G, Poenisch C, Eitel I, Denks D, de Waha S, Pöss J, et al. Prognostic impact of established and novel renal function biomarkers in myocardial infarction with cardiogenic shock: A biomarker substudy of the IABP-SHOCK II-trial. *Int J Cardiol* 2015;**191**:159–166. <https://doi.org/10.1016/j.ijcard.2015.04.242>
34. Schupp T, Rusnak J, Forner J, Weidner K, Ruka M, Egner-Walter S, et al. Cardiac troponin I but not N-terminal pro-B-type natriuretic peptide predicts outcomes in cardiogenic shock. *J Pers Med* 2023;**13**:1348. <https://doi.org/10.3390/jpm13091348>
35. Luyt CE, Landivier A, Leprince P, Bernard M, Pavie A, Chastre J, et al. Usefulness of cardiac biomarkers to predict cardiac recovery in patients on extracorporeal membrane oxygenation support for refractory cardiogenic shock. *J Crit Care* 2012;**27**:524.e7–524.e14. <https://doi.org/10.1016/j.jcrc.2011.12.009>
36. Zochios V, Valchanov K. Raised cardiac troponin in intensive care patients with sepsis, in the absence of angiographically documented coronary artery disease: A systematic review. *J Intensive Care Soc* 2015;**16**:52–57. <https://doi.org/10.1177/1751143714555303>
37. Samuel NA, Roddick A, Glampson B, Mulla A, Davies J, Papadimitriou D, et al. Prognostic significance of troponin in patients with malignancy (NIHR Health Informatics Collaborative TROP-MALIGNANCY study). *Cardiooncology* 2024;**10**:41. <https://doi.org/10.1186/s40959-024-00238-w>
38. Andrié RP, Becher UM, Frommold R, Tiyerili V, Schrickel JW, Nickenig G, et al. Interleukin-6 is the strongest predictor of 30-day mortality in patients with cardiogenic shock due to myocardial infarction. *Crit Care* 2012;**16**:R152. <https://doi.org/10.1186/cc11467>
39. Kataja A, Tarvasmäki T, Lassus J, Sionis A, Mebazaa A, Pulkki K, et al.; CardShock Investigators. Kinetics of procalcitonin, C-reactive protein and interleukin-6 in cardiogenic shock – Insights from the CardShock study. *Int J Cardiol* 2021;**322**:191–196. <https://doi.org/10.1016/j.ijcard.2020.08.069>
40. Picariello C, Lazzari C, Chiostrri M, Gensini GF, Valente S. Kinetic of procalcitonin in patients with cardiogenic shock following acute myocardial infarction: Preliminary data. *HSR Proc Intensive Care Cardiovasc Anesth* 2010;**2**:201–207.
41. Kim DW, Cho HJ, Kim GS, Song SY, Na KJ, Oh SG, et al. Predictive value of procalcitonin for infection and survival in adult cardiogenic shock patients treated with extracorporeal membrane oxygenation. *Chonnam Med J* 2018;**54**:48–54. <https://doi.org/10.4068/cmj.2018.54.1.48>
42. Rajšić S, Tremblé B, Jadzic D, Breitkopf R, Oberleitner C, Popovic Krneta M, et al. Extracorporeal membrane oxygenation for cardiogenic shock: A meta-analysis of mortality and complications. *Ann Intensive Care* 2022;**12**:93. <https://doi.org/10.1186/s13613-022-01067-9>
43. Gregoriano C, Heilmann E, Molitor A, Schuetz P. Role of procalcitonin use in the management of sepsis. *J Thorac Dis* 2020;**12**:S5–S15. <https://doi.org/10.21037/jtd.2019.11.63>
44. Avrillon V, Locatelli-Sanchez M, Folliet L, Carbonnaux M, Perino E, Fossard G, et al. Lung cancer may increase serum procalcitonin level. *Infect Disord Drug Targets* 2015;**15**:57–63. <https://doi.org/10.2174/187152615666150320162950>
45. Shetty NS, Patel N, Parcha V, Vekariya N, Xie R, Arora G, et al. Clinical correlates and prognostic value of B-type natriuretic peptide in left ventricular assist device recipients with cardiogenic shock: Insights from INTERMACS. *Am J Cardiol* 2023;**205**:451–453. <https://doi.org/10.1016/j.amjcard.2023.07.177>
46. Katayama T, Nakashima H, Takagi C, Honda Y, Suzuki S, Yano K. Predictors of mortality in patients with acute myocardial infarction and cardiogenic shock. *Circ J* 2005;**69**:83–88.
47. Sharma YP, Kanabar K, Santosh K, Kasinadhuni G, Krishnappa D. Role of N-terminal pro-B-type natriuretic peptide in the prediction of outcomes in ST-elevation myocardial infarction complicated by cardiogenic shock. *Indian Heart J* 2020;**72**:302–305. <https://doi.org/10.1016/j.ihj.2020.07.002>
48. Rivers EP, McCord J, Otero R, Jacobsen G, Loomba M. Clinical utility of B-type natriuretic peptide in early severe sepsis and septic shock. *J Intensive Care Med* 2007;**22**:363–373. <https://doi.org/10.1177/0885066607307523>
49. Bando S, Soeki T, Matsuura T, Tobiume T, Ise T, Kusunose K, et al. Plasma brain natriuretic peptide levels are elevated in patients with cancer. *PLoS One* 2017;**12**:e0178607. <https://doi.org/10.1371/journal.pone.0178607>
50. Pareek N, Kordis P, Beckley-Hoelscher N, Pimenta D, Kocjanec ST, Jazbec A, et al. A practical risk score for early prediction of neurological outcome after out-of-hospital cardiac arrest: MIRACLE2. *Eur Heart J* 2020;**41**:4508–4517. <https://doi.org/10.1093/eurheartj/ehaa570>
51. Engström M, Schött U, Romner B, Reinstrup P. Acidosis impairs the coagulation: A thromboelastographic study. *J Trauma* 2006;**61**:624–628. <https://doi.org/10.1097/01.ta.0000226739.30655.75>
52. Wengenmayer T, Duerschmied D, Graf E, Chiabudini M, Benk C, Mühlischlegel S, et al. Development and validation of a prognostic model for survival in patients treated with venoarterial extracorporeal membrane oxygenation: The

- PREDICT VA-ECMO score. *Eur Heart J Acute Cardiovasc Care* 2019;**8**:350–359. <https://doi.org/10.1177/2048872618789052>
53. Charbonneau F, Chahinian K, Bebawi E, Lavigneur O, Lévesque É, Lamarche Y, et al. Parameters associated with successful weaning of veno-arterial extracorporeal membrane oxygenation: A systematic review. *Crit Care* 2022;**26**:375. <https://doi.org/10.1186/s13054-022-04249-w>
 54. Iscra F, Gullo A, Biolo G. Bench-to-bedside review: Lactate and the lung. *Crit Care* 2002;**6**:327–329. <https://doi.org/10.1186/cc1519>
 55. Radovic M, Bojic S, Kotur-Stevuljevic J, Lezica V, Milicic B, Velinovic M, et al. Serum lactate as reliable biomarker of acute kidney injury in low-risk cardiac surgery patients. *J Med Biochem* 2019;**38**:118–125. <https://doi.org/10.2478/jomb-2018-0018>
 56. Cheng CY, Kung CT, Wu KH, Chen FC, Cheng HH, Cheng FJ, et al. Liver cirrhosis affects serum lactate level measurement while assessing disease severity in patients with sepsis. *Eur J Gastroenterol Hepatol* 2021;**33**:1201–1208. <https://doi.org/10.1097/MEG.0000000000001826>
 57. Yao YM, Yu Y, Wu Y, Lu LR, Sheng ZY. Plasma D (-)-lactate as a new marker for diagnosis of acute intestinal injury following ischemia-reperfusion. *World J Gastroenterol* 1997;**3**:225–227. <https://doi.org/10.3748/wjg.v3.i4.225>
 58. Engstrom M, Schott U, Nordstrom CH, Romner B, Reinstrop P. Increased lactate levels impair the coagulation system – a potential contributing factor to progressive hemorrhage after traumatic brain injury. *J Neurosurg Anesthesiol* 2006;**18**:200–204. <https://doi.org/10.1097/01.ana.0000211002.63774.8a>
 59. Banerjee D, Perrett C, Banerjee A. Troponins, acute coronary syndrome and renal disease: From acute kidney injury through end-stage kidney disease. *Eur Cardiol* 2019;**14**:187–190. <https://doi.org/10.15420/eur.2019.28.2>
 60. Audimoolam VK, McPhail MJ, Sherwood R, Willars C, Bernal W, Wendon JA, et al. Elevated troponin I and its prognostic significance in acute liver failure. *Crit Care* 2012;**16**:R228. <https://doi.org/10.1186/cc11883>
 61. North M, Eckman P, Samara M, Chavez I, Schmidt C, Garberich R, et al. Peak troponin predicts successful weaning from VA ECMO in patients with acute myocardial infarction complicated by cardiogenic shock. *Int J Artif Organs* 2022;**45**:68–74. <https://doi.org/10.1177/0391398821991155>
 62. Kan WC, Huang YT, Wu VC, Shiao CC. Predictive ability of procalcitonin for acute kidney injury: A narrative review focusing on the interference of infection. *Int J Mol Sci* 2021;**22**:6903. <https://doi.org/10.3390/ijms22136903>
 63. Dong R, Wan B, Lin S, Wang M, Huang J, Wu Y, et al. Procalcitonin and liver disease: A literature review. *J Clin Transl Hepatol* 2019;**7**:51–55. <https://doi.org/10.14218/JCTH.2018.00012>
 64. Cosse C, Sabbagh C, Kamel S, Galmiche A, Regimbeau JM. Procalcitonin and intestinal ischemia: A review of the literature. *World J Gastroenterol* 2014;**20**:17773–17778. <https://doi.org/10.3748/wjg.v20.i47.17773>
 65. Cepkova M, Kapur V, Ren X, Quinn T, Zhuo H, Foster E, et al. Clinical significance of elevated B-type natriuretic peptide in patients with acute lung injury with or without right ventricular dilatation: An observational cohort study. *Ann Intensive Care* 2011;**1**:18. <https://doi.org/10.1186/2110-5820-1-18>
 66. Takase H, Dohi Y. Kidney function crucially affects B-type natriuretic peptide (BNP), N-terminal proBNP and their relationship. *Eur J Clin Invest* 2014;**44**:303–308. <https://doi.org/10.1111/eci.12234>
 67. Sato Y, Yoshihisa A, Takeishi R, Ohara H, Sugawara Y, Ichijo Y, et al. B-type natriuretic peptide is associated with the occurrence of bleeding events in heart failure patients with a history of coronary artery disease. *J Cardiol* 2022;**80**:88–93. <https://doi.org/10.1016/j.jcc.2022.02.003>
 68. Shirakabe A, Matsushita M, Shibata Y, Shighihara S, Nishigoori S, Sawatani T, et al. Organ dysfunction, injury, and failure in cardiogenic shock. *J Intensive Care* 2023;**11**:26. <https://doi.org/10.1186/s40560-023-00676-1>
 69. Attanà P, Lazzeri C, Picariello C, Dini CS, Gensini GF, Valente S. Lactate and lactate clearance in acute cardiac care patients. *Eur Heart J Acute Cardiovasc Care* 2012;**1**:115–121. <https://doi.org/10.1177/2048872612451168>
 70. Slottosch I, Liakopoulos O, Kuhn E, Scherner M, Deppe AC, Sabashnikov A, et al. Lactate and lactate clearance as valuable tool to evaluate ECMO therapy in cardiogenic shock. *J Crit Care* 2017;**42**:35–41. <https://doi.org/10.1016/j.jcrc.2017.06.022>
 71. Tolppanen H, Rivas-Lasarte M, Lassus J, Sans-Roselló J, Hartmann O, Lindholm M, et al. Adrenomedullin: A marker of impaired hemodynamics, organ dysfunction, and poor prognosis in cardiogenic shock. *Ann Intensive Care* 2017;**7**:6. <https://doi.org/10.1186/s13613-016-0229-2>
 72. Buchan TA, Ching C, Foroutan F, Malik A, Daza JF, Hing NNF, et al. Prognostic value of natriuretic peptides in heart failure: Systematic review and meta-analysis. *Heart Fail Rev* 2022;**27**:645–654. <https://doi.org/10.1007/s10741-021-10136-3>
 73. Almeida I, Chin J, Santos H, Miranda H, Santos M, Sá C, et al.; National Cardiology Data Collection Center, Portuguese Society of Cardiology, Coimbra, Portugal, National Register of Acute Coronary Syndromes Investigators. Prognostic value of brain natriuretic peptide in ST-elevation myocardial infarction patients: A Portuguese registry. *Rev Port Cardiol* 2022;**41**:87–95. <https://doi.org/10.1016/j.repc.2020.12.016>
 74. Jaraí R, Fellner B, Haoula D, Jordanova N, Heinz G, Karth GD, et al. Early assessment of outcome in cardiogenic shock: Relevance of plasma N-terminal pro-B-type natriuretic peptide and interleukin-6 levels. *Crit Care Med* 2009;**37**:1837–1844. <https://doi.org/10.1097/CCM.0b013e31819fe896>
 75. Jolly SS, Shenkman H, Brieger D, Fox KA, Yan AT, Eagle KA, et al.; GRACE Investigators. Quantitative troponin and death, cardiogenic shock, cardiac arrest and new heart failure in patients with non-ST-segment elevation acute coronary syndromes (NSTE ACS): Insights from the Global Registry of Acute Coronary Events. *Heart* 2011;**97**:197–202. <https://doi.org/10.1136/hrt.2010.195511>
 76. Dudda J, Schupp T, Rusnak J, Weidner K, Abumayyah M, Ruka M, et al. C-reactive protein and white blood cell count in cardiogenic shock. *J Clin Med* 2023;**12**:965. <https://doi.org/10.3390/jcm12030965>
 77. Sinning CR, Sinning JM, Schulz A, Schnabel RB, Lubos E, Wild PS, et al. Association of serum procalcitonin with cardiovascular prognosis in coronary artery disease. *Circ J* 2011;**75**:1184–1191. <https://doi.org/10.1253/circj.cj-10-0638>
 78. Winzap P, Davies A, Klingenberg R, Obeid S, Roffi M, Mach F, et al. Diabetes and baseline glucose are associated with inflammation, left ventricular function and short- and long-term outcome in acute coronary syndromes: Role of the novel biomarker Cyr 61. *Cardiovasc Diabetol* 2019;**18**:142. <https://doi.org/10.1186/s12933-019-0946-6>
 79. Iborra-Egea O, Rueda F, García-García C, Borrás E, Sabido E, Bayes-Genis A. Molecular signature of cardiogenic shock. *Eur Heart J* 2020;**41**:3839–3848. <https://doi.org/10.1093/eurheartj/ehz783>
 80. Pöss J, Fuernau G, Denks D, Desch S, Eitel I, De Waha S, et al. Angiotensin-2 in acute myocardial infarction complicated by cardiogenic shock – a biomarker substudy of the IABP-SHOCK II-trial. *Eur J Heart Fail* 2015;**17**:1152–1160. <https://doi.org/10.1002/ehfj.342>
 81. Link A, Pöss J, Rbah R, Barth C, Feth L, Selejan S, et al. Circulating angiotensins and cardiovascular mortality in cardiogenic shock. *Eur Heart J* 2013;**34**:1651–1662. <https://doi.org/10.1093/eurheartj/ehs487>
 82. David S, Mukherjee A, Ghosh CC, Yano M, Khankin EV, Wenger JB, et al. Angiotensin-2 may contribute to multiple organ dysfunction and death in sepsis. *Crit Care Med* 2012;**40**:3034–3041. <https://doi.org/10.1097/CCM.0b013e31825fcd31>
 83. Wu X, Giobbie-Hurder A, Liao X, Connelly C, Connolly EM, Li J, et al. Angiotensin-2 as a biomarker and target for immune checkpoint therapy. *Cancer Immunol Res* 2017;**5**:17–28. <https://doi.org/10.1158/2326-6066.CCR-16-0206>
 84. Frydland M, Møller JE, Lindholm MG, Hansen R, Wiberg S, Lerche Helgestad OK, et al. Biomarkers predictive of late cardiogenic shock development in patients with suspected ST-elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2020;**9**:557–566. <https://doi.org/10.1177/2048872619896063>
 85. Gomes DA, De Almeida Beltrão RL, De Oliveira Junior FM, Da Silva Junior JC, De Arruda EPC, Lira EC, et al. Vasopressin and copeptin release during sepsis and septic shock. *Peptides* 2021;**136**:170437. <https://doi.org/10.1016/j.peptides.2020.170437>
 86. Winzler B, Steinmetz M, Refardt J, Cesana-Nigro N, Popovic M, Fenske W, et al. Copeptin is not useful as a marker of malignant disease in the syndrome of inappropriate antidiuresis. *Endocr Connect* 2020;**9**:20–27. <https://doi.org/10.1530/EC-19-0431>
 87. Wenzl FA, Bruno F, Kraler S, Klingenberg R, Akhmedov A, Ministrini S, et al. Dipeptidyl peptidase 3 plasma levels predict cardiogenic shock and mortality in acute coronary syndromes. *Eur Heart J* 2023;**44**:3859–3871. <https://doi.org/10.1093/eurheartj/ehad545>
 88. Blet A, Deniau B, Santos K, Van Lier DPT, Azibani F, Wittebole X, et al.; AdrenOSS-1 Study Investigators. Monitoring circulating dipeptidyl peptidase 3 (DPP3) predicts improvement of organ failure and survival in sepsis: A prospective observational multinational study. *Crit Care* 2021;**25**:61. <https://doi.org/10.1186/s13054-021-03471-2>
 89. Ye P, Duan W, Leng YQ, Wang YK, Tan X, Wang WZ. DPP3: From biomarker to therapeutic target of cardiovascular diseases. *Front Cardiovasc Med* 2022;**9**:974035. <https://doi.org/10.3389/fcvm.2022.974035>
 90. Cheng W, Fuernau G, Desch S, Freund A, Feistritzter HJ, Pöss J, et al. Circulating galectin-3 in patients with cardiogenic shock complicating acute myocardial infarction treated with mild hypothermia: A biomarker sub-study of the SHOCK-COOL trial. *J Clin Med* 2022;**11**:7168. <https://doi.org/10.3390/jcm11237168>
 91. Karabacak P. Serum galectin-3 levels predict poor prognosis in sepsis and septic shock patients. *Rev Assoc Med Bras (1992)* 2023;**69**:e20220940. <https://doi.org/10.1590/1806-9282.20220940>
 92. Wang Y, Liu S, Tian Y, Wang Y, Zhang Q, Zhou X, et al. Prognostic role of galectin-3 expression in patients with solid tumors: A meta-analysis of 36

- eligible studies. *Cancer Cell Int* 2018;**18**:172. <https://doi.org/10.1186/s12935-018-0668-y>
93. Fuernau G, Poenisch C, Eitel I, De Waha S, Desch S, Schuler G, et al. Growth-differentiation factor 15 and osteoprotegerin in acute myocardial infarction complicated by cardiogenic shock: A biomarker substudy of the IABP-SHOCK II-trial. *Eur J Heart Fail* 2014;**16**:880–887. <https://doi.org/10.1002/ehf.117>
 94. Li H, Tang D, Chen J, Hu Y, Cai X, Zhang P. The clinical value of GDF15 and its prospective mechanism in sepsis. *Front Immunol* 2021;**12**:710977. <https://doi.org/10.3389/fimmu.2021.710977>
 95. Modi A, Dwivedi S, Roy D, Khokhar M, Purohit P, Vishnoi J, et al. Growth differentiation factor 15 and its role in carcinogenesis: An update. *Growth Factors* 2019;**37**:190–207. <https://doi.org/10.1080/08977194.2019.1685988>
 96. Lundberg OHM, Lengquist M, Spångfors M, Annborn M, Bergmann D, Schulte J, et al. Circulating bioactive adrenomedullin as a marker of sepsis, septic shock and critical illness. *Crit Care* 2020;**24**:636. <https://doi.org/10.1186/s13054-020-03351-1>
 97. Vázquez R, Riveiro ME, Berenguer-Daizé C, O’Kane A, Gormley J, Touzelet O, et al. Targeting adrenomedullin in oncology: A feasible strategy with potential as much more than an alternative anti-angiogenic therapy. *Front Oncol* 2021;**10**:589218. <https://doi.org/10.3389/fonc.2020.589218>
 98. Lipinska-Gediga M, Mierzchala M, Durek G. Pro-atrial natriuretic peptide (pro-ANP) level in patients with severe sepsis and septic shock: Prognostic and diagnostic significance. *Infection* 2012;**40**:303–309. <https://doi.org/10.1007/s15010-011-0235-0>
 99. Hur M, Kim H, Kim HJ, Yang HS, Magrini L, Marino R, et al. Soluble ST2 has a prognostic role in patients with suspected sepsis. *Ann Lab Med* 2015;**35**:570–577. <https://doi.org/10.3343/alm.2015.35.6.570>
 100. Chang CP, Hu MH, Hsiao YP, Wang YC. ST2 signaling in the tumor microenvironment. *Adv Exp Med Biol* 2020;**1240**:83–93. https://doi.org/10.1007/978-3-030-38315-2_7
 101. Kastl SP, Krychtiuk KA, Lenz M, Distelmaier K, Goliash G, Huber K, et al. Intestinal fatty acid binding protein is associated with mortality in patients with acute heart failure or cardiogenic shock. *Shock* 2019;**51**:410–415. <https://doi.org/10.1097/SHK.0000000000001195>
 102. Sekino M, Funaoka H, Sato S, Okada K, Inoue H, Yano R, et al. Intestinal fatty acid-binding protein level as a predictor of 28-day mortality and bowel ischemia in patients with septic shock: A preliminary study. *J Crit Care* 2017;**42**:92–100. <https://doi.org/10.1016/j.jcrc.2017.07.012>
 103. Hongisto M, Lassus J, Tarvasmäki T, Sans-Roselló J, Tolppanen H, Kataja A, et al.; CardShock Study Investigators and the GREAT Network. Soluble urokinase-type plasminogen activator receptor improves early risk stratification in cardiogenic shock. *Eur Heart J Acute Cardiovasc Care* 2022;**11**:731–738. <https://doi.org/10.1093/ehjacc/zaac096>
 104. Huang Q, Xiong H, Yan P, Shuai T, Liu J, Zhu L, et al. The diagnostic and prognostic value of suPAR in patients with sepsis: A systematic review and meta-analysis. *Shock* 2020;**53**:416–425. <https://doi.org/10.1097/SHK.0000000000001434>
 105. Özdirik B, Stueven A, Knorr J, Geisler L, Mohr R, Demir M, et al. Soluble urokinase plasminogen activator receptor (suPAR) concentrations are elevated in patients with neuroendocrine malignancies. *J Clin Med* 2020;**9**:1647. <https://doi.org/10.3390/jcm9061647>
 106. Martensson J, Martling CR, Oldner A, Bell M. Impact of sepsis on levels of plasma cystatin C in AKI and non-AKI patients. *Nephrol Dial Transplant* 2012;**27**:576–581. <https://doi.org/10.1093/ndt/gfr358>
 107. Jones M, Denieffe S, Griffin C, Tinago W, Fitzgibbon MC. Evaluation of cystatin C in malignancy and comparability of estimates of GFR in oncology patients. *Pract Lab Med* 2017;**8**:95–104. <https://doi.org/10.1016/j.plabm.2017.05.005>
 108. Zhang CF, Wang HJ, Tong ZH, Zhang C, Wang YS, Yang HQ, et al. The diagnostic and prognostic values of serum and urinary kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin in sepsis induced acute renal injury patients. *Eur Rev Med Pharmacol Sci* 2020;**24**:5604–5617. https://doi.org/10.26355/eurrev_202005_21346
 109. Scelo G, Muller DC, Riboli E, Johansson M, Cross AJ, Vineis P, et al. KIM-1 as a blood-based marker for early detection of kidney cancer: A prospective nested case-control study. *Clin Cancer Res* 2018;**24**:5594–5601. <https://doi.org/10.1158/1078-0432.CCR-18-1496>
 110. Vanmassenhove J, Glorieux G, Lameire N, Hoste E, Dhondt A, Vanholder R, et al. Influence of severity of illness on neutrophil gelatinase-associated lipocalin performance as a marker of acute kidney injury: A prospective cohort study of patients with sepsis. *BMC Nephrol* 2015;**16**:18. <https://doi.org/10.1186/s12882-015-0003-y>
 111. Candido S, Maestro R, Polesel J, Catania A, Maira F, Signorelli SS, et al. Roles of neutrophil gelatinase-associated lipocalin (NGAL) in human cancer. *Oncotarget* 2014;**5**:1576–1594. <https://doi.org/10.18632/oncotarget.1738>
 112. Vivas MC, Villamarin Guerrero HF, Tascon AJ, Valderrama-Aguirre A. Plasma interleukin-6 levels correlate with survival in patients with bacterial sepsis and septic shock. *Interv Med Appl Sci* 2021;**11**:224–230. <https://doi.org/10.1556/1646.2020.00006>
 113. Vainer N, Dehrendorff C, Johansen JS. Systematic literature review of IL-6 as a biomarker or treatment target in patients with gastric, bile duct, pancreatic and colorectal cancer. *Oncotarget* 2018;**9**:29820–29841. <https://doi.org/10.18632/oncotarget.25661>
 114. Pöss J, Mahfoud F, Seiler S, Heine GH, Fliser D, Böhm M, et al. FGF-23 is associated with increased disease severity and early mortality in cardiogenic shock. *Eur Heart J Acute Cardiovasc Care* 2013;**2**:211–218. <https://doi.org/10.1177/2048872613494025>
 115. Dounousi E, Torino C, Pizzini P, Cutrupi S, Panuccio V, D’Arrigo G, et al. Intact FGF23 and α -Klotho during acute inflammation/sepsis in CKD patients. *Eur J Clin Invest* 2016;**46**:234–241. <https://doi.org/10.1111/eci.12588>
 116. Ewendt F, Feger M, Föller M. Role of fibroblast growth factor 23 (FGF23) and α Klotho in cancer. *Front Cell Dev Biol* 2021;**8**:601006. <https://doi.org/10.3389/fcell.2020.601006>
 117. Jäntti T, Tarvasmäki T, Harjola VP, Pulkki K, Turkia H, Sabell T, et al.; CardShock Investigators. Predictive value of plasma proenkephalin and neutrophil gelatinase-associated lipocalin in acute kidney injury and mortality in cardiogenic shock. *Ann Intensive Care* 2021;**11**:25. <https://doi.org/10.1186/s13613-021-00814-8>
 118. Kim H, Hur M, Struck J, Bergmann A, Somma SD; GREAT Network. Proenkephalin predicts organ failure, renal replacement therapy, and mortality in patients with sepsis. *Ann Lab Med* 2020;**40**:466–473. <https://doi.org/10.3343/alm.2020.40.6.466>
 119. Ceglarek U, Schellong P, Rosolowski M, Scholz M, Willenberg A, Kratzsch J, et al. The novel cystatin C, lactate, interleukin-6, and N-terminal pro-B-type natriuretic peptide (CLIP)-based mortality risk score in cardiogenic shock after acute myocardial infarction. *Eur Heart J* 2021;**42**:2344–2352. <https://doi.org/10.1093/eurheartj/ehab110>
 120. Rueda F, Borrás E, García-García C, Iborra-Egea O, Revuelta-López E, Harjola VP, et al. Protein-based cardiogenic shock patient classifier. *Eur Heart J* 2019;**40**:2684–2694. <https://doi.org/10.1093/eurheartj/ehz294>
 121. Farshidpour M, Pace S, Volk ML. The clinical value of angiotensin-2 in liver diseases. *Clin Liver Dis (Hoboken)* 2022;**19**:244–247. <https://doi.org/10.1002/cld.1218>
 122. Meijer E, Bakker SJL, De Jong PE, Homan Van Der Heide JJ, Van Son WJ, Struck J, et al. Copeptin, a surrogate marker of vasopressin, is associated with accelerated renal function decline in renal transplant recipients. *Transplantation* 2009;**88**:561–567. <https://doi.org/10.1097/TP.0b013e3181b11ae4>
 123. Dépret F, Amzallag J, Pollina A, Fayolle-Pivot L, Coutrot M, Chaussard M, et al. Circulating dipeptidyl peptidase-3 at admission is associated with circulatory failure, acute kidney injury and death in severely ill burn patients. *Crit Care* 2020;**24**:168. <https://doi.org/10.1186/s13054-020-02888-5>
 124. Humphries DC, Mills R, Boz C, McHugh BJ, Hirani N, Rossi AG, et al. Galectin-3 inhibitor GB0139 protects against acute lung injury by inhibiting neutrophil recruitment and activation. *Front Pharmacol* 2022;**13**:949264. <https://doi.org/10.3389/fphar.2022.949264>
 125. Sun H, Jiang H, Eliaz A, Kellum JA, Peng Z, Eliaz I. Galectin-3 in septic acute kidney injury: A translational study. *Crit Care* 2021;**25**:109. <https://doi.org/10.1186/s13054-021-03538-0>
 126. An Y, Xu S, Liu Y, Xu X, Phillips CA, Chen J, et al. Role of galectins in the liver diseases: A systematic review and meta-analysis. *Front Med* 2021;**8**:744518. <https://doi.org/10.3389/fmed.2021.744518>
 127. Jakobs K, Rauch U. Galectin-3 inhibitors as novel antithrombotic drugs with almost no bleeding risk: Wishful thinking or a realistic vision? *Eur Heart J* 2022;**43**:3575–3577. <https://doi.org/10.1093/eurheartj/ehac128>
 128. Coletti K, Griffiths M, Nies M, Brandal S, Everett AD, Bembea MM. Cardiac dysfunction biomarkers are associated with potential for successful separation from extracorporeal membrane oxygenation in children. *ASAIO J* 2023;**69**:198–204. <https://doi.org/10.1097/MAT.0000000000001759>
 129. Jiang WW, Zhang ZZ, He PP, Jiang LP, Chen JZ, Zhang XT, et al. Emerging roles of growth differentiation factor-15 in brain disorders (review). *Exp Ther Med* 2021;**22**:1270. <https://doi.org/10.3892/etm.2021.10705>
 130. Heringlake M, Charitos EI, Erber K, Berggreen AE, Heinze H, Paarmann H. Preoperative plasma growth-differentiation factor-15 for prediction of acute kidney injury in patients undergoing cardiac surgery. *Crit Care* 2016;**20**:317. <https://doi.org/10.1186/s13054-016-1482-3>
 131. Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Eikelboom JW, Ezekowitz MD, et al. Growth-differentiation factor 15 and risk of major bleeding in atrial fibrillation: Insights from the Randomized Evaluation of Long-Term Anticoagulation therapy (RE-LY) trial. *Am Heart J* 2017;**190**:94–103. <https://doi.org/10.1016/j.ahj.2017.06.001>

132. Lacquaniti A, Ceresa F, Campo S, Barbera G, Caruso D, Palazzo E, et al. Acute kidney injury and sepsis after cardiac surgery: The roles of tissue inhibitor metalloproteinase-2, insulin-like growth factor binding protein-7, and mid-regional pro-adrenomedullin. *J Clin Med* 2023;**12**:5193. <https://doi.org/10.3390/jcm12165193>
133. Roth GA, Zimmermann M, Lubczyk BA, Pilz J, Faybik P, Hetz H, et al. Up-regulation of interleukin 33 and soluble ST2 serum levels in liver failure. *J Surg Res* 2010;**163**:e79–e83. <https://doi.org/10.1016/j.jss.2010.04.004>
134. Yu L, Wu X, Wang H, Long D, Yang J, Zhang Y. Diagnostic and prognostic significance of suPAR in traumatic brain injury. *Neural India* 2014;**62**:498–502. <https://doi.org/10.4103/0028-3886.144439>
135. Huang Y, Huang S, Zhuo X, Lin M. Predictive value of suPAR in AKI: A systematic review and meta-analysis. *Clin Exp Nephrol* 2023;**27**:1–11. <https://doi.org/10.1007/s10157-022-02300-2>
136. Wei C, Zhu K, Reiser J. Soluble urokinase receptor and liver disease. *Clin Liver Dis* 2019;**14**:163–166. <https://doi.org/10.1002/cld.850>
137. Lind M, Jansson JH, Nilsson TK, Järholm LS, Johansson L. Cystatin C and creatinine as markers of bleeding complications, cardiovascular events and mortality during oral anticoagulant treatment. *Thromb Res* 2013;**132**:e77–e82. <https://doi.org/10.1016/j.thromres.2013.06.011>
138. Montagnana M, Danese E, Lippi G. Biochemical markers of acute intestinal ischemia: Possibilities and limitations. *Ann Transl Med* 2018;**6**:341. <https://doi.org/10.21037/atm.2018.07.22>
139. Neyra JA, Hu MC, Moe OW. Fibroblast growth factor 23 and α Klotho in acute kidney injury: Current status in diagnostic and therapeutic applications. *Nephron* 2020;**144**:665–672. <https://doi.org/10.1159/000509856>
140. Fischer JP, Els-Heindl S, Beck-Sickingler AG. Adrenomedullin – current perspective on a peptide hormone with significant therapeutic potential. *Peptides* 2020;**131**:170347. <https://doi.org/10.1016/j.peptides.2020.170347>
141. Geven C, Kox M, Pickkers P. Adrenomedullin and adrenomedullin-targeted therapy as treatment strategies relevant for sepsis. *Front Immunol* 2018;**9**:292. <https://doi.org/10.3389/fimmu.2018.00292>
142. Khan SQ, O'Brien RJ, Struck J, Quinn P, Morgenthaler N, Squire I, et al. Prognostic value of midregional pro-adrenomedullin in patients with acute myocardial infarction: The LAMP (Leicester Acute Myocardial Infarction Peptide) study. *J Am Coll Cardiol* 2007;**49**:1525–1532. <https://doi.org/10.1016/j.jacc.2006.12.038>
143. Sugo S, Minamino N, Shoji H, Kangawa K, Kitamura K, Eto T, et al. Interleukin-1, tumor necrosis factor and lipopolysaccharide additively stimulate production of adrenomedullin in vascular smooth muscle cells. *Biochem Biophys Res Commun* 1995;**207**:25–32. <https://doi.org/10.1006/bbrc.1995.1148>
144. Lassus J, Gayat E, Mueller C, Peacock WF, Spinar J, Harjola VP, et al.; GREAT-Network. Incremental value of biomarkers to clinical variables for mortality prediction in acutely decompensated heart failure: The Multinational Observational Cohort on Acute Heart Failure (MOCA) study. *Int J Cardiol* 2013;**168**:2186–2194. <https://doi.org/10.1016/j.ijcard.2013.01.228>
145. Voordes G, Davison B, Biegus J, Edwards C, Damman K, Ter Maaten J, et al. Biologically active adrenomedullin as a marker for residual congestion and early rehospitalization in patients hospitalized for acute heart failure: Data from STRONG-HF. *Eur J Heart Fail* 2024;**26**:1480–1492. <https://doi.org/10.1002/ehf.3336>
146. Takagi K, Levy B, Kimmoun A, Miró Ò, Duarte K, Asakage A, et al. Elevated plasma bioactive adrenomedullin and mortality in cardiogenic shock: Results from the OptimaCC trial. *J Clin Med* 2021;**10**:4512. <https://doi.org/10.3390/jcm10194512>
147. Nishikimi T, Saito Y, Kitamura K, Ishimitsu T, Eto T, Kangawa K, et al. Increased plasma levels of adrenomedullin in patients with heart failure. *J Am Coll Cardiol* 1995;**26**:1424–1431. [https://doi.org/10.1016/0735-1097\(95\)00338-X](https://doi.org/10.1016/0735-1097(95)00338-X)
148. Marino R, Struck J, Maisel AS, Magrini L, Bergmann A, Somma S. Plasma adrenomedullin is associated with short-term mortality and vasopressor requirement in patients admitted with sepsis. *Crit Care* 2014;**18**:R34. <https://doi.org/10.1186/cc13731>
149. Pang X, Shimizu A, Kurita S, Zankov DP, Takeuchi K, Yasuda-Yamahara M, et al. Novel therapeutic role for dipeptidyl peptidase III in the treatment of hypertension. *Hypertension* 2016;**68**:630–641. <https://doi.org/10.1161/HYPERTENSIONAHA.116.07357>
150. Frigyesi A, Lengquist M, Spångfors M, Annborn M, Cronberg T, Nielsen N, et al. Circulating dipeptidyl peptidase 3 on intensive care unit admission is a predictor of organ dysfunction and mortality. *J Intensive Care* 2021;**9**:52. <https://doi.org/10.1186/s40560-021-00561-9>
151. Takagi K, Blet A, Levy B, Deniau B, Azibani F, Feliot E, et al. Circulating dipeptidyl peptidase 3 and alteration in haemodynamics in cardiogenic shock: Results from the OptimaCC trial. *Eur J Heart Fail* 2020;**22**:279–286. <https://doi.org/10.1002/ehf.1600>
152. Innelli P, Lopizzo T, Paternò G, Bruno N, Radice RP, Bertini P, et al. Dipeptidyl amino-peptidase 3 (DPP3) as an early marker of severity in a patient population with cardiogenic shock. *Diagnostics* 2023;**13**:1350. <https://doi.org/10.3390/diagnostics13071350>
153. Winzap PA, Kraler S, Obeid S, Wenzl FA, Templin C, Klingenberg R, et al.; SPUM-ACS Investigators. Initial systolic blood pressure associates with systemic inflammation, myocardial injury, and outcomes in patients with acute coronary syndromes. *Eur Heart J Acute Cardiovasc Care* 2023;**12**:437–450. <https://doi.org/10.1093/ehjacc/zuad047>
154. Bruno F, Adjibodou B, Obeid S, Kraler SC, Wenzl FA, Akhtar MM, et al. Occlusion of the infarct-related coronary artery presenting as acute coronary syndrome with and without ST-elevation: Impact of inflammation and outcomes in a real-world prospective cohort. *Eur Heart J Qual Care Clin Outcomes* 2023;**9**:564–574. <https://doi.org/10.1093/ehjqcco/qcad027>
155. Sandek A, Bjarnason I, Volk HD, Crane R, Meddings JB, Niebauer J, et al. Studies on bacterial endotoxin and intestinal absorption function in patients with chronic heart failure. *Int J Cardiol* 2012;**157**:80–85. <https://doi.org/10.1016/j.ijcard.2010.12.016>
156. Kitai T, Kim YH, Kiefer K, Morales R, Borowski AG, Grodin JL, et al. Circulating intestinal fatty acid-binding protein (I-FABP) levels in acute decompensated heart failure. *Clin Biochem* 2017;**50**:491–495. <https://doi.org/10.1016/j.clinbiochem.2017.02.014>
157. Piton G, Belon F, Cypriani B, Regnard J, Puyraveau M, Manzoni C, et al. Enterocyte damage in critically ill patients is associated with shock condition and 28-day mortality. *Crit Care Med* 2013;**41**:2169–2176. <https://doi.org/10.1097/CCM.0b013e31828c26b5>
158. Nguyen Dinh Cat A, Touyz RM. Cell signaling of angiotensin II on vascular tone: Novel mechanisms. *Curr Hypertens Rep* 2011;**13**:122–128. <https://doi.org/10.1007/s11906-011-0187-x>
159. Akwii RG, Sajib MS, Zahra FT, Mikelis CM. Role of angiotensin-2 in vascular physiology and pathophysiology. *Cells* 2019;**8**:471. <https://doi.org/10.3390/cells8050471>
160. Thanh Duyen LT, Manh BV, Phuong Thao TT, Khanh LV, Linh Trang BN, Giang NT, et al. Prognostic significance of the angiotensin-2 for early prediction of septic shock in severe sepsis patients. *Future Sci OA* 2022;**8**:FSO825. <https://doi.org/10.2144/fsoa-2022-0077>
161. Eleuteri E, Di Stefano A, Tarro Genta F, Vicari C, Gnemmi I, Colombo M, et al. Stepwise increase of angiotensin-2 serum levels is related to haemodynamic and functional impairment in stable chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2011;**18**:607–614. <https://doi.org/10.1177/1741826710389410>
162. Lorbeer R, Baumeister SE, Dörr M, Nauck M, Grotevendt A, Völzke H, et al. Circulating angiotensin-2, its soluble receptor Tie-2, and mortality in the general population. *Eur J Heart Fail* 2013;**15**:1327–1334. <https://doi.org/10.1093/eurjhf/hft117>
163. Fincke R, Hochman JS, Lowe AM, Menon V, Slater JN, Webb JG, et al.; SHOCK Investigators. Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: A report from the SHOCK trial registry. *J Am Coll Cardiol* 2004;**44**:340–348. <https://doi.org/10.1016/j.jacc.2004.03.060>
164. Finkel MS, Oddis CV, Jacob TD, Watkins SC, Hattler BG, Simmons RL. Negative inotropic effects of cytokines on the heart mediated by nitric oxide. *Science* 1992;**257**:387–389. <https://doi.org/10.1126/science.1631560>
165. Larsson TE. The role of FGF-23 in CKD-MBD and cardiovascular disease: Friend or foe? *Nephrol Dial Transplant* 2010;**25**:1376–1381. <https://doi.org/10.1093/ndt/gfp784>
166. Kendrick J, Cheung AK, Kaufman JS, Greene T, Roberts WL, Smits G, et al.; HOST Investigators. FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. *J Am Soc Nephrol* 2011;**22**:1913–1922. <https://doi.org/10.1681/ASN.2010121224>
167. Ix JH, Katz R, Kestenbaum BR, De Boer IH, Chonchol M, Mukamal KJ, et al. Fibroblast growth factor-23 and death, heart failure, and cardiovascular events in community-living individuals. *J Am Coll Cardiol* 2012;**60**:200–207. <https://doi.org/10.1016/j.jacc.2012.03.040>
168. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, et al. FGF23 induces left ventricular hypertrophy. *J Clin Invest* 2011;**121**:4393–4408. <https://doi.org/10.1172/JCI46122>
169. Musgrove J, Wolf M. Regulation and effects of FGF23 in chronic kidney disease. *Annu Rev Physiol* 2020;**82**:365–390. <https://doi.org/10.1146/annurev-physiol-021119-034650>
170. Schumacher D, Alampour-Rajabi S, Ponomarev V, Curaj A, Wu Z, Staudt M, et al. Cardiac FGF23: New insights into the role and function of FGF23 after acute myocardial infarction. *Cardiovasc Pathol* 2019;**40**:47–54. <https://doi.org/10.1016/j.carpath.2019.02.001>
171. Dieplinger B, Mueller T. Soluble ST2 in heart failure. *Clin Chim Acta* 2015;**443**:57–70. <https://doi.org/10.1016/j.cca.2014.09.021>

172. Broch K, Ueland T, Nymo SH, Kjekshus J, Hulthe J, Muntendam P, et al.; CORONA Study Group. Soluble ST2 is associated with adverse outcome in patients with heart failure of ischaemic aetiology. *Eur J Heart Fail* 2012;**14**:268–277. <https://doi.org/10.1093/eurjhf/hfs006>
173. Weinberg EO, Shimpo M, De Keulenaer GW, MacGillivray C, Tominaga S, Solomon SD, et al. Expression and regulation of ST2, an interleukin-1 receptor family member, in cardiomyocytes and myocardial infarction. *Circulation* 2002;**106**:2961–2966. <https://doi.org/10.1161/01.cir.0000038705.69871.d9>
174. Tolppanen H, Rivas-Lasarte M, Lassus J, Sadoune M, Gayat E, Pulkki K, et al.; CardShock Investigators. Combined measurement of soluble ST2 and amino-terminal pro-B-type natriuretic peptide provides early assessment of severity in cardiogenic shock complicating acute coronary syndrome. *Crit Care Med* 2017;**45**:e666–e673. <https://doi.org/10.1097/CCM.0000000000002336>
175. Shao C, Cao Y, Wang Z, Wang X, Li C, Hao X, et al. Soluble ST2 predicts continuous renal replacement therapy in patients receiving venoarterial extracorporeal membrane oxygenation. *Perfusion* 2024;**39**:927–934. <https://doi.org/10.1177/02676591231169410>
176. Parenica J, Malaska J, Jarkovsky J, Lipkova J, Dastych M, Helanova K, et al. Soluble ST2 levels in patients with cardiogenic and septic shock are not predictors of mortality. *Exp Clin Cardiol* 2012;**17**:205–209.
177. Mahmood N, Mihalciou C, Rabbani SA. Multifaceted role of the Urokinase-type plasminogen activator (uPA) and its receptor (uPAR): Diagnostic, prognostic, and therapeutic applications. *Front Oncol* 2018;**8**:24. <https://doi.org/10.3389/fonc.2018.00024>
178. Kanno Y. The uPA/uPAR system orchestrates the inflammatory response, vascular homeostasis, and immune system in fibrosis progression. *Int J Mol Sci* 2023;**24**:1796. <https://doi.org/10.3390/ijms24021796>
179. Thunø M, Macho B, Eugen-Olsen J. uPAR: The molecular crystal ball. *Dis Markers* 2009;**27**:157–172. <https://doi.org/10.3233/DMA-2009-0657>
180. Velissaris D, Zareifopoulos N, Koniari I, Karamouzou V, Bousis D, Gerarakis A, et al. Soluble urokinase plasminogen activator receptor as a diagnostic and prognostic biomarker in cardiac disease. *J Clin Med Res* 2021;**13**:133–142. <https://doi.org/10.14740/jocmr4459>
181. Jäntti T, Tarvasmäki T, Harjola VP, Parissis J, Pulkki K, Sionis A, et al. Frequency and prognostic significance of abnormal liver function tests in patients with cardiogenic shock. *Am J Cardiol* 2017;**120**:1090–1097. <https://doi.org/10.1016/j.amjcard.2017.06.049>
182. Sheikh O, Nguyen T, Bansal S, Prasad A. Acute kidney injury in cardiogenic shock: A comprehensive review. *Catheter Cardiovasc Interv* 2021;**98**:E91–E105. <https://doi.org/10.1002/ccd.29141>
183. Obaid S, Youisif N, Davies A, Loretz R, Saleh L, Niederseer D, et al. Prognostic role of plasma galectin-3 levels in acute coronary syndrome. *Eur Heart J Acute Cardiovasc Care* 2020;**9**:869–878. <https://doi.org/10.1177/2048872620974612>
184. Ichimura T, Bonventre JV, Bailly V, Wei H, Hession CA, Cate RL, et al. Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury. *J Biol Chem* 1998;**273**:4135–4142. <https://doi.org/10.1074/jbc.273.7.4135>
185. Han WK, Bailly V, Abichandani R, Thadhani R, Bonventre JV. Kidney injury molecule-1 (KIM-1): A novel biomarker for human renal proximal tubule injury. *Kidney Int* 2002;**62**:237–244. <https://doi.org/10.1046/j.1523-1755.2002.00433.x>
186. Shao X, Tian L, Xu W, Zhang Z, Wang C, Qi C, et al. Diagnostic value of urinary kidney injury molecule 1 for acute kidney injury: A meta-analysis. *PLoS One* 2014;**9**:e84131. <https://doi.org/10.1371/journal.pone.0084131>
187. Khreba NA, Abdelsalam M, Wahab AM, Sanad M, Elhelaly R, Adel M, et al. Kidney injury molecule 1 (KIM-1) as an early predictor for acute kidney injury in post-cardiopulmonary bypass (CPB) in open heart surgery patients. *Int J Nephrol* 2019;**2019**:6265307. <https://doi.org/10.1155/2019/6265307>
188. Schulz CA, Engström G, Nilsson J, Almgren P, Petkovic M, Christensson A, et al. Plasma kidney injury molecule-1 (p-KIM-1) levels and deterioration of kidney function over 16 years. *Nephrol Dial Transplant* 2020;**35**:265–273. <https://doi.org/10.1093/ndt/gfy382>
189. Mori K, Nakao K. Neutrophil gelatinase-associated lipocalin as the real-time indicator of active kidney damage. *Kidney Int* 2007;**71**:967–970. <https://doi.org/10.1038/sj.ki.5002165>
190. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: A systematic review and meta-analysis. *Am J Kidney Dis* 2009;**54**:1012–1024. <https://doi.org/10.1053/j.ajkd.2009.07.020>
191. Emmens JE, Ter Maaten JM, Damman K, Van Veldhuisen DJ, De Boer RA, Struck J, et al. Proenkephalin, an opioid system surrogate, as a novel comprehensive renal marker in heart failure. *Circ Heart Fail* 2019;**12**:e005544. <https://doi.org/10.1161/CIRCHEARTFAILURE.118.005544>
192. Beunders R, Struck J, Wu AHB, Zarbock A, Di Somma S, Mehta RL, et al. Proenkephalin (PENK) as a novel biomarker for kidney function. *J Appl Lab Med* 2017;**2**:400–412. <https://doi.org/10.1373/jalm.2017.023598>
193. Kim H, Hur M, Lee S, Marino R, Magrini L, Cardelli P, et al.; GREAT Network. Proenkephalin, neutrophil gelatinase-associated lipocalin, and estimated glomerular filtration rates in patients with sepsis. *Ann Lab Med* 2017;**37**:388–397. <https://doi.org/10.3343/alm.2017.37.5.388>
194. Wang G, Bonkovsky HL, De Lemos A, Burczynski FJ. Recent insights into the biological functions of liver fatty acid binding protein 1. *J Lipid Res* 2015;**56**:2238–2247. <https://doi.org/10.1194/jlr.R056705>
195. Coe NR, Bernlohr DA. Physiological properties and functions of intracellular fatty acid-binding proteins. *Biochim Biophys Acta* 1998;**1391**:287–306. [https://doi.org/10.1016/s0005-2760\(97\)00205-1](https://doi.org/10.1016/s0005-2760(97)00205-1)
196. Atshaves BP, Storey SM, Petrescu A, Greenberg CC, Lyuksyutova OI, Smith R, et al. Expression of fatty acid binding proteins inhibits lipid accumulation and alters toxicity in L cell fibroblasts. *Am J Physiol Cell Physiol* 2002;**283**:C688–C703. <https://doi.org/10.1152/ajpcell.00586.2001>
197. Asaka M, Miyazaki T, Hollinger FB, Alpert E. Human aldolase B serum levels: A marker of liver injury. *Hepatology* 1984;**4**:531–535. <https://doi.org/10.1002/hep.1840040329>
198. Möckel M, Muller R, Searle J, Slagman A, De Bruyne B, Serruys P, et al. Usefulness of beta2-microglobulin as a predictor of all-cause and nonculprit lesion-related cardiovascular events in acute coronary syndromes (from the PROSPER study). *Am J Cardiol* 2015;**116**:1034–1040. <https://doi.org/10.1016/j.amjcard.2015.07.017>
199. Barton KT, Kakajiwala A, Dietzen DJ, Goss CW, Gu H, Dharnidharka VR. Using the newer kidney disease: Improving global outcomes criteria, beta-2-microglobulin levels associate with severity of acute kidney injury. *Clin Kidney J* 2018;**11**:797–802. <https://doi.org/10.1093/ckj/sfy056>
200. Davis A, Lu F, Mejia P. C1 inhibitor, a multi-functional serine protease inhibitor. *Thromb Haemost* 2010;**104**:886–893. <https://doi.org/10.1160/TH10-01-0073>
201. Dettling A, Weimann J, Sundermeyer J, Beer BN, Besch L, Becher PM, et al. Association of systemic inflammation with shock severity, 30-day mortality, and therapy response in patients with cardiogenic shock. *Clin Res Cardiol* 2024;**113**:324–335. <https://doi.org/10.1007/s00392-023-02336-8>
202. Fattouch K, Bianco G, Speziale G, Sampognaro R, Lavalle C, Guccione F, et al. Beneficial effects of C1 esterase inhibitor in ST-elevation myocardial infarction in patients who underwent surgical reperfusion: A randomised double-blind study. *Eur J Cardiothorac Surg* 2007;**32**:326–332. <https://doi.org/10.1016/j.ejcts.2007.04.038>
203. Thiele H, Akin I, Sandri M, Fuernau G, De Waha S, Meyer-Saraei R, et al.; CULPRIT-SHOCK Investigators. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med* 2017;**377**:2419–2432. <https://doi.org/10.1056/NEJMoa1710261>
204. West M, Kirby A, Stewart RA, Blankenberg S, Sullivan D, White HD, et al. Circulating cystatin C is an independent risk marker for cardiovascular outcomes, development of renal impairment, and long-term mortality in patients with stable coronary heart disease: The LIPID study. *J Am Heart Assoc* 2022;**11**:e020745. <https://doi.org/10.1161/JAHA.121.020745>
205. Helmersson-Karlqvist J, Lipcsey M, Årnlov J, Bell M, Ravn B, Dardashti A, et al. Addition of cystatin C predicts cardiovascular death better than creatinine in intensive care. *Heart* 2022;**108**:279–284. <https://doi.org/10.1136/heartjnl-2020-318860>
206. Ravn B, Prowle JR, Mårtensson J, Martling CR, Bell M. Superiority of serum cystatin C over creatinine in prediction of long-term prognosis at discharge from ICU. *Crit Care Med* 2017;**45**:e932–e940. <https://doi.org/10.1097/CCM.0000000000000537>
207. Wasyanto T, Yasa A, Yudhistira Y. Cystatin C as a predictor of major adverse cardiovascular event in patients with acute myocardial infarction without cardiogenic shock and renal impairment after coronary intervention. *Int J Gen Med* 2023;**16**:2219–2227. <https://doi.org/10.2147/IJGM.S415595>
208. Salgado JV, Souza FL, Salgado BJ. How to understand the association between cystatin C levels and cardiovascular disease: Imbalance, counterbalance, or consequence? *J Cardiol* 2013;**62**:331–335. <https://doi.org/10.1016/j.jcc.2013.05.015>
209. Frendéus KH, Wallin H, Janciauskienė S, Abrahamson M. Macrophage responses to interferon-gamma are dependent on cystatin C levels. *Int J Biochem Cell Biol* 2009;**41**:2262–2269. <https://doi.org/10.1016/j.biocel.2009.05.005>
210. Deniau B, Picod A, Azibani F, Gayat E, Mebazaa A, Blet A. The CLIP-based mortality score in cardiogenic shock: Suitable only for cardiogenic shock? *Eur J Heart Fail* 2021;**23**:1240–1242. <https://doi.org/10.1002/ehf.2208>
211. Diakos NA, Thayer K, Swain L, Goud M, Jain P, Kapur NK. Systemic inflammatory burden correlates with severity and predicts outcomes in patients with cardiogenic shock supported by a percutaneous mechanical assist device. *J Cardiovasc Trans Res* 2021;**14**:476–483. <https://doi.org/10.1007/s12265-020-10078-5>
212. Tseng CCS, Huibers MMH, Gaykema LH, Siera-de Koning E, Ramjankhan FZ, Maisel AS, et al. Soluble ST2 in end-stage heart failure, before and after support

- with a left ventricular assist device. *Eur J Clin Invest* 2018;**48**:e12886. <https://doi.org/10.1111/eci.12886>
213. Opfermann P, Simader E, Felli A, Bevilacqua M, Holaubek C, Dworschak M, et al. Early sT2 liberation after implantation of a left ventricular assist device in patients with advanced heart failure. *J Immunol Res* 2020;**2020**:5826176. <https://doi.org/10.1155/2020/5826176>
 214. Cheng R, Hachamovitch R, Kittleson M, Patel J, Arabia F, Moriguchi J, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: A meta-analysis of 1,866 adult patients. *Ann Thorac Surg* 2014;**97**:610–616. <https://doi.org/10.1016/j.athoracsur.2013.09.008>
 215. Batchelor RJ, Wheelahan A, Zheng WC, Stub D, Yang Y, Chan W. Impella versus Venoarterial extracorporeal membrane oxygenation for acute myocardial infarction cardiogenic shock: A systematic review and meta-analysis. *J Clin Med* 2022;**11**:3955. <https://doi.org/10.3390/jcm11143955>
 216. Kanji R, Vandenbrielle C, Arachchilage DRJ, Price S, Gorog DA. Optimal tests to minimise bleeding and ischaemic complications in patients on extracorporeal membrane oxygenation. *Thromb Haemost* 2022;**122**:480–491. <https://doi.org/10.1055/a-1508-8230>
 217. Flierl U, Tongers J, Berliner D, Sieweke JT, Zauner F, Wingert C, et al. Acquired von Willebrand syndrome in cardiogenic shock patients on mechanical circulatory microaxial pump support. *PLoS One* 2017;**12**:e0183193. <https://doi.org/10.1371/journal.pone.0183193>
 218. Van Edom CJ, Gramegna M, Baldetti L, Beneduce A, Castelein T, Dauwe D, et al. Management of bleeding and hemolysis during percutaneous microaxial flow pump support: A practical approach. *JACC Cardiovasc Interv* 2023;**16**:1707–1720. <https://doi.org/10.1016/j.jcin.2023.05.043>
 219. Sharma A, Stevens SR, Lucas J, Fuzat M, Adams KF, Whellan DJ, et al. Utility of growth differentiation factor-15, a marker of oxidative stress and inflammation, in chronic heart failure: Insights from the HF-ACTION study. *JACC Heart Fail* 2017;**5**:724–734. <https://doi.org/10.1016/j.jchf.2017.07.013>
 220. Mathews L, Hu X, Ding N, Ishigami J, Al Rifai M, Hoogeveen RC, et al. Growth differentiation factor 15 and risk of bleeding events: The Atherosclerosis Risk in Communities study. *J Am Heart Assoc* 2023;**12**:e023847. <https://doi.org/10.1161/JAHA.121.023847>
 221. Rossaint J, Vestweber D, Zarbock A. GDF-15 prevents platelet integrin activation and thrombus formation. *J Thromb Haemost* 2013;**11**:335–344. <https://doi.org/10.1111/jth.12100>
 222. Hagström E, James SK, Bertilsson M, Becker RC, Himmelmann A, Husted S, et al.; PLATO Investigators. Growth differentiation factor-15 level predicts major bleeding and cardiovascular events in patients with acute coronary syndromes: Results from the PLATO study. *Eur Heart J* 2016;**37**:1325–1333. <https://doi.org/10.1093/eurheartj/ehv491>
 223. Hongisto M, Kataja A, Tarvasmäki T, Holopainen A, Javanainen T, Jurkko R, et al. Levels of growth differentiation factor 15 and early mortality risk stratification in cardiogenic shock. *J Card Fail* 2019;**25**:894–901. <https://doi.org/10.1016/j.cardfail.2019.07.003>
 224. Nakamura M, Imamura T, Ueno H, Kinugawa K. Impact of the elevated angiotensin-2 levels during Impella support on the short-term prognosis. *J Artif Organs* 2023;**26**:184–191. <https://doi.org/10.1007/s10047-022-01347-y>
 225. Hultström M, Fromell K, Larsson A, Persson B, Nilsson B, Quaggin SE, et al. Angiotensin-2 inhibition of thrombomodulin-mediated anticoagulation – a novel mechanism that may contribute to hypercoagulation in critically ill COVID-19 patients. *Biomedicines* 2022;**10**:1333. <https://doi.org/10.3390/biomedicines10061333>
 226. Hobohm L, Kölmel S, Niemann C, Kumpers P, Krieg VJ, Bochenek ML, et al. Role of angiotensin-2 in venous thrombus resolution and chronic thromboembolic disease. *Eur Respir J* 2021;**58**:2004196. <https://doi.org/10.1183/13993003.04196-2020>
 227. Chen Y, Fu W, Zheng Y, Yang J, Liu Y, Qi Z, et al. Galectin 3 enhances platelet aggregation and thrombosis via dectin-1 activation: A translational study. *Eur Heart J* 2022;**43**:3556–3574. <https://doi.org/10.1093/eurheartj/ehac034>
 228. Coromilas E, Que-Xu EC, Moore D, Kato TS, Wu C, Ji R, et al. Dynamics and prognostic role of galectin-3 in patients with advanced heart failure, during left ventricular assist device support and following heart transplantation. *BMC Cardiovasc Disord* 2016;**16**:138. <https://doi.org/10.1186/s12872-016-0298-z>
 229. Kharga K, Kumar L, Patel SKS. Recent advances in monoclonal antibody-based approaches in the management of bacterial sepsis. *Biomedicines* 2023;**11**:765. <https://doi.org/10.3390/biomedicines11030765>
 230. Durán-Méndez A, Aguilar-Arroyo AD, Vivanco-Gómez E, Nieto-Ortega E, Pérez-Ortega D, Jiménez-Pérez C, et al. Tocilizumab reduces COVID-19 mortality and pathology in a dose and timing-dependent fashion: A multi-centric study. *Sci Rep* 2021;**11**:19728. <https://doi.org/10.1038/s41598-021-99291-z>
 231. Meyer MAS, Wiberg S, Grand J, Meyer ASP, Obling LER, Frydland M, et al. Treatment effects of Interleukin-6 receptor antibodies for modulating the systemic inflammatory response after out-of-hospital cardiac arrest (the IMICA trial): A double-blinded, placebo-controlled, single-center, randomized, clinical trial. *Circulation* 2021;**143**:1841–1851. <https://doi.org/10.1161/CIRCULATIONAHA.120.053318>
 232. Bo Kunkel J, Frydland M, Duus Holle S, Kjaergaard J, Pecini R, Evi Bang L, et al. Low-dose dobutamine infusion and single-dose tocilizumab in acute myocardial infarction patients with high risk of cardiogenic shock development – rationale and design of the DOBERMANN trial. *Eur Heart J Acute Cardiovasc Care* 2023;**12**:zuad036.131. <https://doi.org/10.1093/ehjacc/zuad036.131>
 233. Thielmann M, Marggraf G, Neuhauser M, Forkel J, Herold U, Kamler M, et al. Administration of C1-esterase inhibitor during emergency coronary artery bypass surgery in acute ST-elevation myocardial infarction. *Eur J Cardiothorac Surg* 2006;**30**:285–293. <https://doi.org/10.1016/j.ejcts.2006.04.022>
 234. Deniau B, Rehfeld L, Santos K, Dienelt A, Azibani F, Sadoune M, et al. Circulating dipeptidyl peptidase 3 is a myocardial depressant factor: Dipeptidyl peptidase 3 inhibition rapidly and sustainably improves haemodynamics. *Eur J Heart Fail* 2020;**22**:290–299. <https://doi.org/10.1002/ehf.1601>
 235. Sciacaluga C, Mandoli GE, Ghionzoli N, Anselmi F, Dini CS, Righini F, et al. Risk stratification in cardiogenic shock: A focus on the available evidence. *Heart Fail Rev* 2022;**27**:1105–1117. <https://doi.org/10.1007/s10741-021-10140-7>
 236. Tran P, Joshi M, Banerjee P, Otabor E, Adeyeye S, Kuehl M. Important lessons from cardiogenic shock deaths with insight into normotensive cardiogenic shock, the trajectory of SCAI shock severity and timing of referrals for mechanical circulatory support. *Heart* 2023;**109**:A152–A154. <https://doi.org/10.1136/heartjnl-2023-BCS.133>
 237. Delmas C, Bonnefoy E, Puymirat E, Leurent G, Manzo-Silberman S, Elbaz M, et al. Patients near to cardiogenic shock (CS) but without hypotension have similar prognosis when compared to patients with classic CS: Is it time for redefine CS? A FRENDSHOCK multicenter registry analysis. *Arch Cardiovasc Dis Suppl* 2019;**11**:e301. <https://doi.org/10.1016/j.acvdsp.2019.01.027>
 238. Waksman R, Pahuja M, van Diepen S, Proudfoot AG, Morrow D, Spitzer E, et al. Standardized definitions for cardiogenic shock research and mechanical circulatory support devices: Scientific expert panel from the Shock Academic Research Consortium (SHARC). *Circulation* 2023;**148**:1113–1126. <https://doi.org/10.1161/CIRCULATIONAHA.123.064527>
 239. Haertel F, Lehmann T, Heller T, Fritzenwanger M, Pfeifer R, Kretzschmar D, et al. Impact of a VA-ECMO in combination with an extracorporeal cytokine hemadsorption system in critically ill patients with cardiogenic shock – design and rationale of the ECMOSorb trial. *J Clin Med* 2023;**12**:4893. <https://doi.org/10.3390/jcm12154893>
 240. See KC. Personalizing care for critically ill adults using omics: A concise review of potential clinical applications. *Cells* 2023;**12**:541. <https://doi.org/10.3390/cells12040541>
 241. Baum L, Kokot K, Erbe S, Kneuer J, Buettner P, Thiele H, et al. Regulation of circular RNAs in patients with cardiogenic shock. *Eur Heart J* 2023;**44**:ehad655.3050. <https://doi.org/10.1093/eurheartj/ehad655.3050>
 242. Yuan Y, Li X, Chu Y, Ye G, Yang L, Dong Z. Long non-coding RNA H19 augments hypoxia/reoxygenation-induced renal tubular epithelial cell apoptosis and injury by the miR-130a/BCL2L11 pathway. *Front Physiol* 2021;**12**:632398. <https://doi.org/10.3389/fphys.2021.632398>
 243. Cortes D, Pera MF. The genetic basis of inter-individual variation in recovery from traumatic brain injury. *NPJ Regen Med* 2021;**6**:5. <https://doi.org/10.1038/s41536-020-00114-y>
 244. Zhang Z, Chen L, Liu H, Sun Y, Shui P, Gao J, et al.; CMAISE Consortium. Gene signature for the prediction of the trajectories of sepsis-induced acute kidney injury. *Crit Care* 2022;**26**:398. <https://doi.org/10.1186/s13054-022-04234-3>
 245. Gorzynski JE, Goenka SD, Shafin K, Jensen TD, Fisk DG, Grove ME, et al. Ultra-rapid nanopore whole genome genetic diagnosis of dilated cardiomyopathy in an adolescent with cardiogenic shock. *Circ Genom Precis Med* 2022;**15**:e003591. <https://doi.org/10.1161/CIRCGEN.121.003591>
 246. Wenzl FA, Fox KAA, Lüscher TF. Towards personalized cardiovascular care: Global Registry of Acute Coronary Events 3.0 score heralds artificial intelligence era. *Eur Heart J* 2023;**44**:4615–4616. <https://doi.org/10.1093/eurheartj/ehad597>
 247. Simons N, Debray FG, Schaper NC, Kooi ME, Feskens EJM, Hollak CEM, et al. Patients With Aldolase B Deficiency Are Characterized by Increased Intrahepatic Triglyceride Content. *J Clin Endocrinol Metab* 2019;**104**(11):5056–5064.
 248. Dong R, Zhang M, Hu Q, Zheng S, Soh A, Zheng Y, et al. Galectin-3 as a novel biomarker for disease diagnosis and a target for therapy (Review). *Int J Mol Med* 2018;**41**(2):599–614.
 249. Bemtgen X, Rilinger J, Jäckel M, Zotzmann V, Supady A, Benk C, et al. Admission blood glucose level and outcome in patients requiring venoarterial extracorporeal membrane oxygenation. *Clin Res Cardiol* 2021;**110**(9):1484–1492.