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RESEARCH ARTICLE

Circulating dipeptidyl peptidase 3 and alteration in haemodynamics in cardiogenic shock: results from the OptimaCC trial

Koji Takagi[1], Alice Blet[1,2], Bruno Levy[3], Benjamin Deniau[1,2], Feriel Azibani[1], Elodie Feliot[1,2], Andreas Bergmann[4], Karine Santos[4], Oliver Hartmann[4], Etienne Gayat[1,2,5], Alexandre Mebazaa[1,2,5]*, and Antoine Kimmoun[1,3]

[1]Inserm UMR-S 942, Cardiovascular Markers in Stress Conditions (MASCOT), University of Paris, Paris, France; [2]Department of Anaesthesiology, Burn and Critical Care, University Hospitals Saint-Louis–Lariboisière, AP-HP, Paris, France; [3]Intensive Care Medicine Brabois, CHRU de Nancy, INSERM U1116, 54511, Vandoeuvre-les-Nancy, Université de Lorraine, Nancy, France; [4]4TEEN4 Pharmaceuticals GmbH, Hennigsdorf, Germany; and [5]Université de Paris, Paris, France

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Aims Dipeptidyl peptidase 3 (DPP3) is a protease involved in the degradation of cardiovascular mediators. Its administration has been shown to be associated with impaired cardiac contraction and kidney haemodynamics while its inhibition restored cardiac contraction in a pre-clinical model of severe heart failure in mice. Circulating DPP3 (cDPP3) was found to be elevated in shock. The present study aims to assess the association between cDPP3 and worsening haemodynamics, namely refractory shock, in a cohort of cardiogenic shock (CS).

Methods and results This is an ancillary study of OptimaCC, a prospective, double-blind, multicentre, randomized study assessing efficacy and safety of catecholamines in 57 patients with CS after acute myocardial infarction. cDPP3 was measured in plasma at inclusion, 24 h, 48 h, and 72 h, and haemodynamic and biological parameters were recorded at inclusion. cDPP3 values were higher in refractory CS than non-refractory CS at inclusion (median [interquartile range]; 76.1 [37.9–238.7] ng/mL vs. 32.8 [23.9–47.6] ng/mL, $P = 0.014$), at 24 h ($P < 0.001$) and up to 48 h ($P = 0.027$). Furthermore, cDPP3 at inclusion discriminated CS patients who did develop refractory shock vs. non-refractory with an area under the curve of 0.73 (95% confidence interval [CI] 0.55–0.92). The high cDPP3 group (cDPP3 ≥59.1 ng/mL) at inclusion had a higher Simplified Acute Physiology Score II (SAPS II), lower cardiac index and lower estimated glomerular filtration rate. More importantly, in CS patients with high cDPP3 at inclusion, those who rapidly decreased cDPP3 at 24 h exhibited a striking reduction in the occurrence of refractory shock and death.

Conclusion In CS patients, cDPP3 gives an early prediction of outcome, including development of refractory status and/or survival. Clinical Trial Registration: clinicaltrials.gov Identifier NCT01367743

Keywords Biomarkers • Cardiogenic shock • Outcome

Introduction

Cardiogenic shock (CS) could be defined as a persistent low cardiac output state resulting in arterial hypotension, organ hypoperfusion, and hyperlactataemia.[1–3] Though aetiologies of CS are numerous, acute myocardial infarction (AMI) is found in 80%.[1,4] Refractory CS, the most severe form of CS, appears in the hours or days following intensive care unit (ICU) admission and has no consensual definition.[5] However, it is recognized that CS not responding to increasing doses of inotrope and vasopressor despite optimal preload could be considered as refractory. Pathophysiology of refractory CS includes an extremely low cardiac output and

*Corresponding author. Department of Anaesthesiology, Burn and Critical Care, University Hospitals Saint-Louis–Lariboisière, AP-HP, Paris, France. Tel: +33 1 49958071, Fax: +33 1 49958073, Email: alexandre.mebazaa@aphp.fr

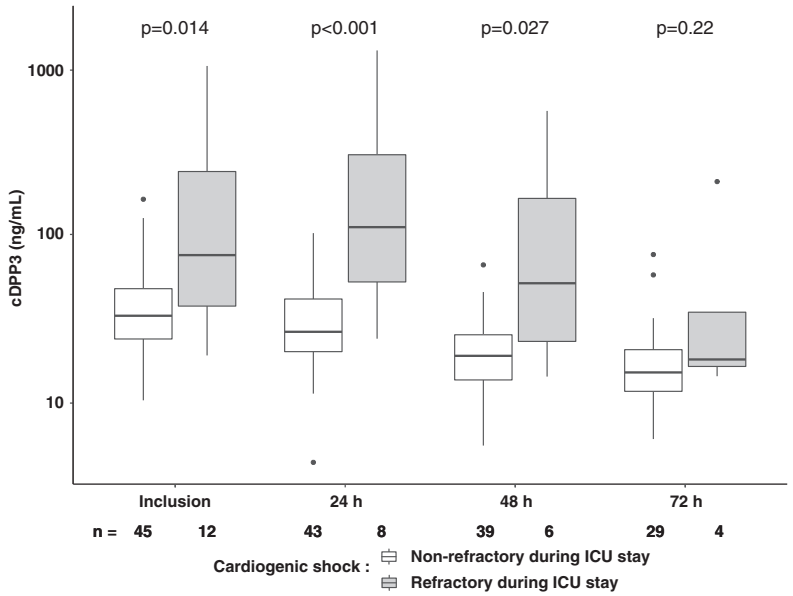

Figure 1 Comparison of the time-course of circulating dipeptidyl peptidase 3 (cDPP3), from inclusion to 72 h, between those that evolved into refractory shock during intensive care unit (ICU) stay and those that did not. A base-10 log scale is used for the *y*-axis. Comparisons at each time point were performed using the Kruskal–Wallis test comparing cDPP3 values in non-refractory cardiogenic shock vs. cDPP3 in refractory cardiogenic shock.

a high level of inflammation impairing the metabolism of endogenous vasoconstrictors, namely catecholamines, vasopressin and/or angiotensin II.[6] Despite advanced management, including aetiological treatment and mechanical circulatory support (MCS), the mortality rate of refractory CS in ICU remains unacceptably high, higher than 50%.[7]

Several scores including the SAVE score, ENCOURAGE score, and modified SAVE score were developed to predict the mortality of refractory CS in patients already on MCS.[8–10] In contrast, no tools have yet been developed to predict worsening from CS to refractory CS. An early risk stratification for patients with CS is crucial to refer patients to the right healthcare centre, to avoid the occurrence of organ dysfunction and initiate, if necessary, MCS.[11,12] With this in mind, few biomarkers have been proved to be beneficial in risk stratification of patients with CS. For instance, lactate, the standard measure of tissue hypoxia, is a biomarker of organ failure that is too late.[13–15] Circulating dipeptidyl peptidase 3 (cDPP3) is a protease involved in the degradation of angiotensin II and enkephalins.[16–18] Recently, it has been shown that high values of cDPP3 were found in critically ill patients suffering from septic shock[19] and CS.[20] We hypothesize that cDPP3 might be associated with alterations in haemodynamics and survival in CS patients.

Methods

Study design

This study is an ancillary analysis from the OptimaCC trial. The study was approved by the Nancy hospital institutional review board and was registered on clinicaltrial.gov (NCT01367743). The princeps study was a multicentre, double-blind, randomized trial of 57 patients conducted in France between September 2011 and August 2016 that compared the use of epinephrine vs. norepinephrine in patients with CS after AMI.

The primary outcome was the change in cardiac index and the secondary outcomes were changes in other haemodynamic variables, cardiac power index, lactate levels, lactate clearance, biomarker levels, and Sequential Organ Failure Assessment (SOFA) score evolution. A detailed description of the study design and main results have been previously published.[21] Of note, in 2015 the safety monitoring board reported a significant imbalance between the epinephrine and norepinephrine groups for the occurrence of refractory CS. This safety event led to the early termination of the study in 2016 with 57/80 patients included.

Participants and inclusion, non-inclusion criteria in the princeps study

Inclusion criteria were adult patients with a CS due to AMI treated by percutaneous coronary intervention. CS was defined by systolic arterial pressure <90 mmHg or mean arterial pressure <65 mmHg without vasopressor or need for vasopressors to correct hypotension, cardiac index <2.2 L/min/m^2 in the absence of vasopressor or inotrope therapy, and at least one evidence of tissue hypoperfusion. On pulmonary artery catheterization, pulmonary artery occlusion pressure had to be >15 mmHg or echocardiography had to evidence high filling pressure. Left ventricular ejection fraction had to be <40% on echocardiography without inotrope support. Non-inclusion criteria were mainly: shock of other origin; immediate indication for MCS; cardiac arrest with early signs of cerebral anoxia; and septic, toxic, and obstructive cardiomyopathy. Refractory CS was previously defined[21]

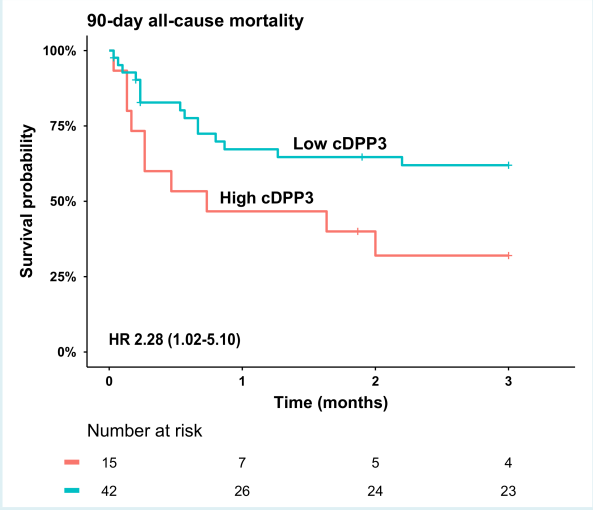

Figure 2 Kaplan–Meier analysis of 90-day all-cause mortality in cardiogenic shock patients with, at inclusion, high (circulating dipeptidyl peptidase 3 [cDPP3] ≥59.1 ng/mL, third quartile) vs. low cDPP3 values (cDPP3 <59.1 ng/mL). HR, hazard ratio.

as a CS with major cardiac dysfunction assessed according to echocardiography, elevated lactate level, acute deterioration of organ function despite the use of >1 μg/kg/min of epinephrine/norepinephrine or dobutamine >10 μg/kg/min and/or intra-aortic balloon support and sustained hypotension (systolic arterial pressure <90 mmHg or mean arterial pressure <65 mmHg) despite adequate intravascular volume.

Study endpoints

For this ancillary study, the primary endpoint was to assess the association between cDPP3 and the occurrence of refractory CS. Secondary endpoints included 90-day all-cause mortality and relationships between cDPP3, and haemodynamic and biological parameters.

Study treatment and protocol

The initial protocol was detailed in the princeps paper.[21] In summary, patients with CS already treated by a vasopressor had to be randomized in the 6 h following the initiation of this vasopressor. After initiation of the study drug, the initial open-label vasopressor was discontinued. The study drug could be switched to an open-label vasopressor in the case of refractory CS as defined above or refractory arrhythmias. The patient was considered to be weaned from the study drug after 24 h without any vasopressor support. Haemodynamic variables were collected closely during the first 72 h. Biological variables were collected daily during the first 7 days and thereafter on days 14, 21, and 28. All-cause mortality was recorded until 90 days. cDPP3 measurements were achieved, blinded from clinical data, in the laboratories of 4TEEN4 Therapeutics GmbH (Hennigsdorf, Germany) in samples collected at inclusion, 24 h, 48 h, and 72 h.

Statistical analyses

Analytical data are the median with 25th and 75th percentiles (median [interquartile range]) for continuous variables, whereas categorical variables are presented as numbers and percentages. Comparisons of inclusion characteristics according to groups were conducted by using Mann–Whitney or Kruskal–Wallis tests for continuous variables and the Fisher exact test or χ^2 test for categorical variables. Cox proportional-hazards regression was used to analyse the effect of cDPP3 and other variables on survival in univariable analyses. Serial biomarker data were analysed by time-dependent Cox regression analysis, and the added value was determined via nested models. Biomarker data was log-transformed. The concordance index (C index) is given as an effect measure. It is equivalent to the concept of area under the curve (AUC) adopted for binary outcome. For illustration, survival curves were drawn according to the third quartile values by using the Kaplan–Meier method. The predictive value of cDPP3, lactate, and SOFA score for the occurrence of refractory CS was estimated by a receiver-operating characteristic curve analysis. A two-sided *P*-value <0.05 was regarded as statistically significant. Statistical analyses were performed using R, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Population characteristics

A total of 57 patients with CS were studied, including 12 patients that developed refractory CS during ICU stay. The characteristics of the population at inclusion according to the occurrence of refractory CS during ICU stay are presented in *Table S1* in the Supplementary material online. Briefly, refractory CS patients compared with non-refractory CS patients had higher age (78 [70–83] years vs. 66 [54–74] years, $P = 0.016$), were mainly female (75% vs. 22%, $P = 0.002$), had higher Simplified Acute Physiology Score II (SAPS II) (74 [57–78] vs. 52 [43–65], $P = 0.016$), higher aspartate transaminase (AST) (1209 [558–1660] IU/L vs. 428 [189–696] IU/L, $P = 0.011$) and higher lactataemia (5.4 [5.1–5.9] mmol/L vs. 3.0 [2.2–5.2] mmol/L, $P = 0.038$). Ninety-day all-cause mortality rate was higher in refractory CS patients compared with non-refractory CS patients (100% vs. 29%, $P < 0.001$).

Circulating dipeptidyl peptidase 3 time-course in refractory and non-refractory shock

Figure 1 shows that cDPP3 values (global coefficient of variation: 193.4%) were higher in refractory CS than non-refractory CS at inclusion (76.1 [37.9–238.7] ng/mL vs. 32.8 [23.9–47.6] ng/mL, $P = 0.014$), at 24 h ($P < 0.001$) and up to 48 h ($P = 0.027$). To discriminate patients who did develop refractory CS from those who did not, cDPP3 at inclusion had an AUC of 0.73 (95% confidence interval [CI] 0.55–0.92). For comparison, lactate at inclusion had an AUC of 0.71 (95% CI 0.57–0.85) and the SOFA score an AUC of 0.61 (95% CI 0.42–0.81). Of note, there was no influence of the vasopressor infused, epinephrine or norepinephrine, on cDPP3 values at any time point (online supplementary *Figure S1*).

Table 1 Comparison of characteristics of cardiogenic shock patients between high circulating dipeptidyl peptidase 3 and low circulating dipeptidyl peptidase 3 groups at inclusion

Variables	Missing values	High cDPP3 at inclusion (n = 15)	Low cDPP3 at inclusion (n = 42)	P-value
Randomization arm				0.72
Epinephrine	0 (0%)	6 (40%)	21 (50%)	
Norepinephrine	0 (0%)	9 (60%)	21 (50%)	
Demographics				
Age (years)	0 (0%)	75 [63–80]	66 [54–76]	0.18
Female sex	0 (0%)	7 (47%)	12 (29%)	0.34
Cardiovascular history				
Hypertension	0 (0%)	6 (40%)	8 (19%)	0.20
Diabetes	0 (0%)	2 (13%)	4 (10%)	0.65
Stroke	0 (0%)	2 (13%)	2 (5%)	0.28
Myocardial infarction	0 (0%)	2 (13%)	2 (5%)	0.28
Severity scores				
SAPS II	1 (2%)	74 [57–80]	48 [43–61]	**0.001**
SOFA score	0 (0%)	11 [9–12]	9 [8–12]	0.19
Clinical presentation at inclusion				
Body mass index (kg/m^2)	3 (5%)	26.6 [22.6–27.6]	24.7 [22.1–27.4]	0.58
Heart rate (bpm)	0 (0%)	91 [74–102]	100 [84–112]	0.14
SVRI (dyne*s*cm^{-5}*m^2)	18 (32%)	3001 [2077–3518]	2333 [1871–2633]	0.20
SvO_2 (%)	6 (11%)	69 [51–74]	72 [65–79]	0.32
Mechanical ventilation	6 (11%)	11 (100%)	35 (88%)	0.57
LVEF (%)	5 (9%)	34 [30–38]	35 [25–40]	0.89
ST-segment elevation	0 (0%)	15 (100%)	40 (95%)	1.00
Laboratory findings at inclusion				
NT-proBNP (pg/mL)	1 (2%)	5275 [1585–15 834]	1846 [562–5972]	0.23
Outcome				
Refractory cardiogenic shock	0 (0%)	7 (47%)	5 (12%)	**0.014**
MCS implantation	0 (0%)	2 (13%)	2 (5%)	0.28
Death within 28 days	3 (5%)	8 (53%)	13 (31%)	0.22
Death within 90 days	5 (9%)	10 (67%)	15 (36%)	0.077

Data are presented as median [IQR] or n (%).
High cDPP3 corresponds to cDPP3 ≥59.1 ng/mL (third quartile) and low cDPP3 corresponds to <59.1 ng/mL.
cDPP3, circulating dipeptidyl peptidase 3; IQR, interquartile range; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; SvO_2, mixed venous oxygen saturation; SVRI, systemic vascular resistance index.

Association of early circulating dipeptidyl peptidase 3 values and outcome

Among the 57 patients included, 25 (44%) died within 90 days (online supplementary *Table S2*). cDPP3 values were greater in the first 48 h in 90-day non-survivors than survivors (online supplementary *Figure S2*). Cox regression analysis found an association between the values of cDPP3 at inclusion and 90-day mortality (C index: 0.603, P = 0.034) but no association with the SOFA score, lactate, or high-sensitivity troponin T (hs-TnT) (all $P > 0.05$). When analysing 90-day risk of death by quartile of cDPP3, *Figure S3* in the supplementary material online shows similar risk of death for the first three quartiles of cDPP3, combined under the name 'low cDPP3' (cDPP3 <59.1 ng/mL) and a greater risk of death for the fourth quartile of cDPP3 (high cDPP3 group, cDPP3 ≥59.1 ng/mL): unadjusted hazard ratio (HR) 2.28 (1.02–5.10) (*Figure 2*).

The characteristics of the population at inclusion according to the third quartile of cDPP3 are presented in *Table 1* and *Figure 3*. Briefly, patients in the high cDPP3 group had higher SAPS II (74 [57–80] vs. 48 [43–61], P = 0.001), similar mean arterial pressure (68 [64–89] mmHg vs. 72 [68–83] mmHg, P = 0.68), lower cardiac index (1.7 [1.2–2.1] L/min/m^2 vs. 2.1 [1.8–2.6] L/min/m^2, P = 0.037), higher hs-TnT (20.7 [6.9–36.6] pg/mL vs. 4.5 [1.9–14.7] pg/mL, P = 0.012), similar lactate (4.3 [2.9–5.2] mmol/L vs. 3.7 [2.0–5.9] mmol/L, P = 0.55), lower estimated glomerular filtration rate (42.6 [27.2–53.3] mL/min vs. 55.9 [40.1–85.9] mL/min, P = 0.010), and higher AST (772 [438–1178] IU/L vs. 428 [164–668] IU/L, P = 0.017) compared with the low cDPP3 group (*Table 1* and *Figure 3*).

Some patients exhibited marked variations in cDPP3 values during the first 24 h after inclusion that led to a change in outcome. Indeed, patients with a high concentration of cDPP3 at inclusion but a low concentration at 24 h (high to low group, HL) had a striking reduction in refractory CS occurrence and reduced 90-day mortality compared with patients with high and sustained cDPP3 values (high to high group, HH) (*Figure 4*). In contrast, patients with

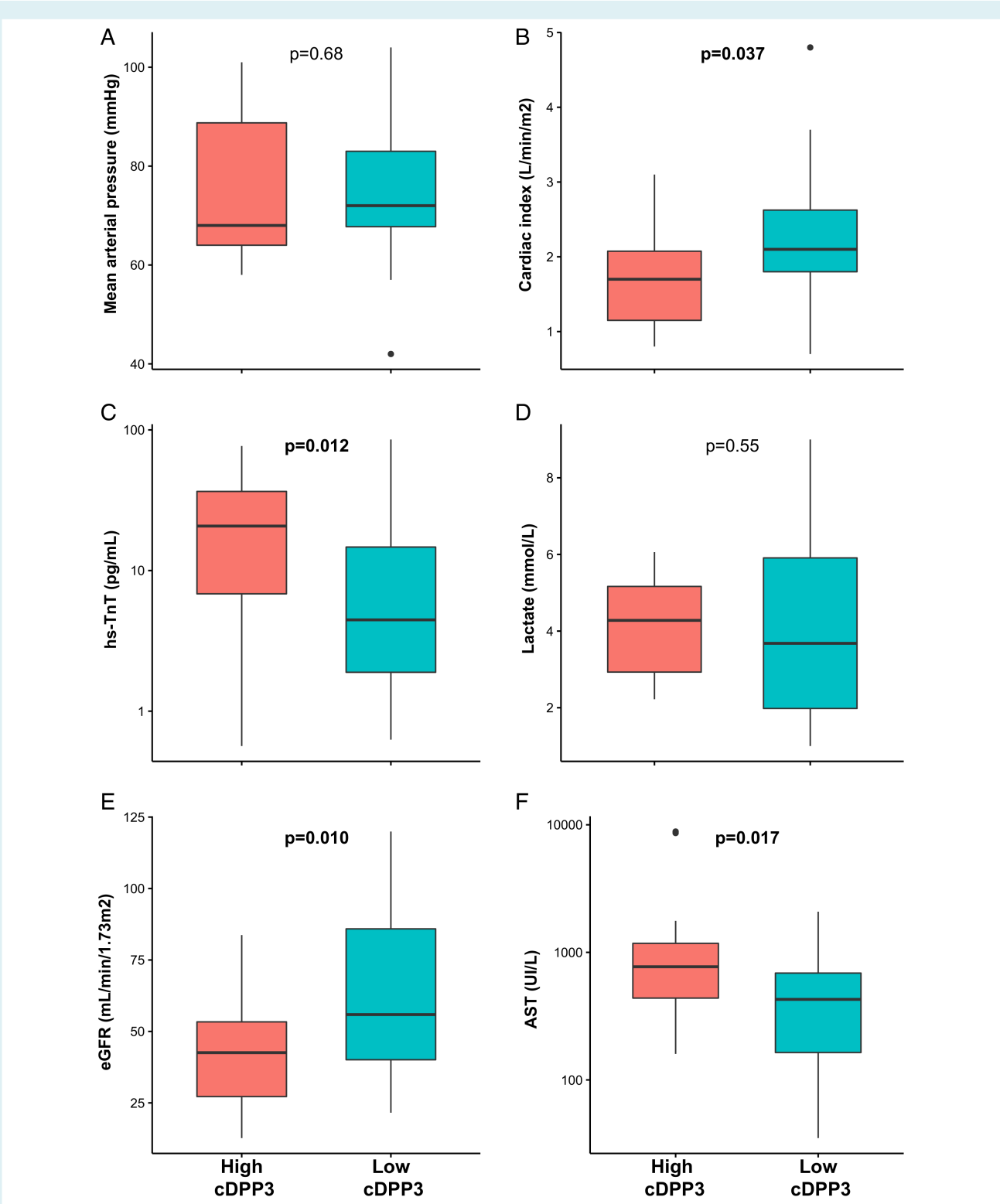

Figure 3 Comparison of haemodynamic and biological variables between cardiogenic shock patients with high and low circulating dipeptidyl peptidase 3 (cDPP3) values at inclusion. A base-10 log scale is used for the *y*-axis for high-sensitivity troponin T (hs-TnT) and aspartate transaminase (AST). eGFR, estimated glomerular filtration rate.

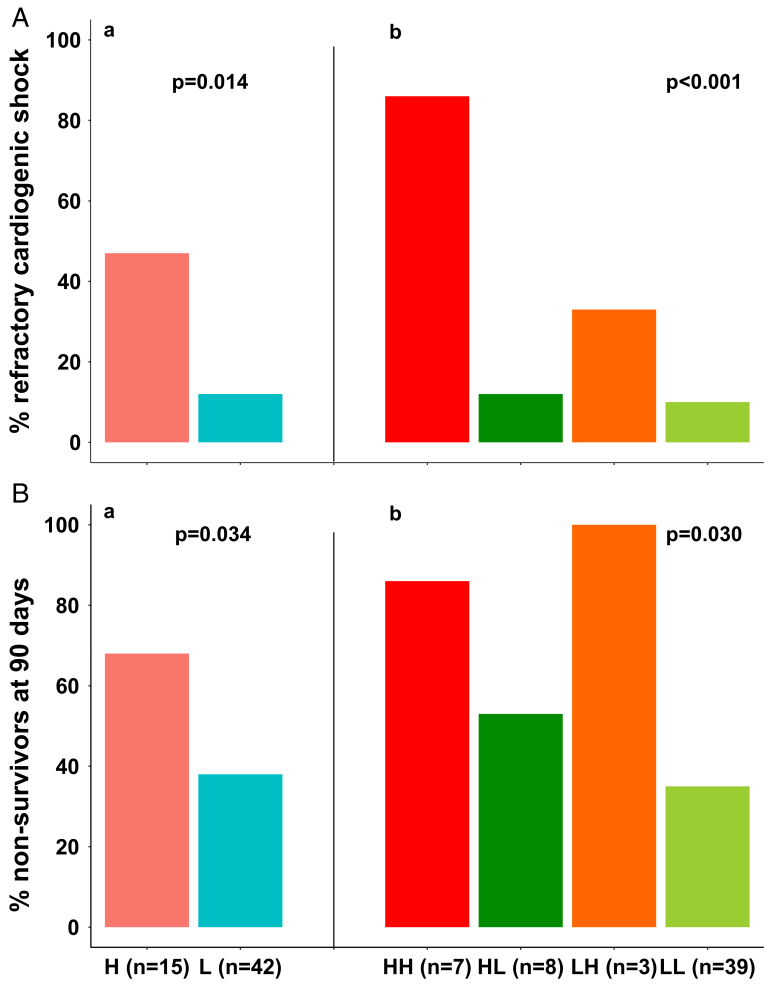

Figure 4 Incremental properties of circulating dipeptidyl peptidase 3 (cDPP3) values at 24 h for prediction of refractory cardiogenic shock (*A*) and 90-day all-cause mortality (*B*; estimated via Kaplan–Meier and Cox regression). cDPP3 categorized into high (H) or low (L) at inclusion based on the third quartile (*a*) and categorized based on cDPP3 at inclusion and 24 h (*b*). HH, cDPP3 above the third quartile (59.1 ng/mL) on inclusion and at 24 h. HL, above the third quartile on inclusion but below the third quartile at 24 h; LL, below the third quartile on inclusion and at 24 h; LH, below the third quartile on inclusion but above the third quartile at 24 h. Patients with missing data at 24 h remained in the category assigned at inclusion.

low cDPP3 at inclusion and increased values at 24 h (low to high group, LH) had a marked increase in mortality when compared with patients with low and sustained cDPP3 values (low to low group, LL) (HR 6.33 [1.28–31.30]) (*Figure 4*).

Discussion

The present study showed that high cDPP3 measured in CS patients at ICU admission was associated with high rate of worsening haemodynamics, namely refractory shock, especially for those who had a persistent elevation of cDPP3 in the day following admission, while those for whom cDPP3 levels rapidly dropped exhibited a striking improvement in outcome.

OptimaCC is a homogeneous and severe population of CS with low cardiac index despite high doses of catecholamines at ICU admission.[21] This presentation reflected the current definition of CS, which was associated with a high degree of inflammation and vasoplegia.[2,6,22] In line with this clinical presentation, mortality rate was also similar to previously published studies.[4,23–25] Some of those patients present a worsened clinical condition during the initial days and develop refractory CS. The latter is defined as CS with persistent high dose of vasopressor(s).[26–28] Recently, worsening CS was also classified as category D (deteriorating/doom) with the need of an escalating number or intensity of intravenous therapies to address hypoperfusion or addition of MCS.[29] Our study shows that two early measures of cDPP3 at inclusion and a day later may indicate either a potential need for escalating therapies if cDPP3 is continuously high or de-escalating therapies if high cDPP3 at ICU admission rapidly returns toward normal values. Accordingly, cDPP3 might add to clinical and haemodynamic parameters and lactate to decide on the escalation or de-escalation of aggressive therapies in CS patients.

DPP3 is a cytosolic enzyme involved in the cleavage of cardiovascular mediators. The present study confirms the previous observation that CS patients with high cDPP3 have worse haemodynamics, renal function, and mortality rate.[20] Though association between high cDPP3 and occurrence of refractory shock remains unknown, a recent publication from our group showed that intravenous administration of DPP3 immediately depressed cardiac contraction while DPP3 inhibition restored cardiac contraction in a heart failure mouse model.[20] Our present study suggests that, in patients with CS, high values of cDPP3 may induce striking negative inotropic action that worsen the already impaired cardiac contraction and lead to refractory shock.

We found that high cDPP3 in the two consecutive days following admission was associated with bad outcomes while a drop in cDPP3 from high to low values was associated with a more favourable outcome. DPP3 is mainly an intracellular protein with a short half-life.[20] Accordingly, it could be suggested that persistent elevation of cDPP3 in some CS patients may be related to high cell death (necrosis) compared with CS patients who normalized cDPP3 values. Finally, inhibition of cDPP3 that may rapidly reduce cDPP3 activity might be beneficial by improving haemodynamic parameters in CS patients, as recently shown in an animal model.[20]

Limitations

We acknowledge several limitations in this study. Firstly, our results must be viewed as a post hoc analysis of a previously published study performed in nine centres, only in France, with other primary endpoints. Accordingly, the results found will need to be confirmed in further multi-national studies with pre-specified endpoints. Secondly, there were major differences in management between patients who went on to develop refractory shock and those who recovered. Thirdly, physiological functions and metabolism of cDPP3 are still poorly understood. For instance, the impact of acute kidney injury on cDPP3 metabolism is unknown. Likewise, previous medications by angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker before the occurrence of CS were not recorded. The impact of these medications on cDPP3 metabolism are unknown and will need further studies. Fourthly, due to the small sample size, we were unable to perform adjusted survival analysis. Finally, future studies should confirm the value of repeated cDPP3 measurements.

Conclusions

The present study demonstrates that cDPP3 may predict early alteration in haemodynamics in CS patients. Though very early high cDPP3 has a bad prognostic value, a rapid normalization of cDPP3 values in the first day indicates a low rate of refractory shock and high survival.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Comparison of characteristics of CS patients, at inclusion, between those that evolved into refractory shock during ICU stay or those that did not.
Table S2. Comparison of characteristics of CS patients between 90-day survivors and non-survivors.
Figure S1. Comparison of time-course of cDPP3, from inclusion to 72 h, between epinephrine group and norepinephrine group.
Figure S2. Comparison of time-course of cDPP3, from inclusion to 72 h, between 90-day survivors and non-survivors.
Figure S3. Kaplan–Meier analysis of 90-day all-cause mortality by quartile for cDPP3 at inclusion.

Acknowledgements

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Conflict of interest: K.T. received speaker's honoraria from Otsuka, Sumitomo Dainippon, AstraZeneca, and Bayer and consultancy fees from Terumo. B.L. received lecture fees from Pulsion, Baxter, Orion, and Lilly; and has received consultant fees from Novartis, Orion, and Baxter. E.G. received a research grant from Sphingotec and consultancy fees from Magnisense and Roche Diagnostics. A.M. reports personal fees from Novartis, Orion, Roche, Servier, Sanofi, Otsuka, Philips, grants and personal fees from Adrenomed, Abbott, grants from 4TEEN4 and A.M. owns fewer than 3000 euros shares of S-Form Pharma company. A.K. received speaker's honoraria from Baxter, MSD, and Gilead. B.D. and A.Bl. were invited to a meeting in Henningsdorf by 4TEEN4 Pharmaceuticals GmbH. K.S. is employed at 4TEEN4 Pharmaceuticals. A.B. is CEO and shareholder at 4TEEN4 Pharmaceuticals. 4TEEN4 owns intellectual properties related to diagnostic use of DPP3. The other authors declared no potential conflicts of interest with respect to the research authorship and/or publication of this article.

References

1. Hollenberg SM, Kavinsky CJ, Parrillo JE. Cardiogenic shock. *Ann Intern Med* 1999;**131**:47–59.
2. Reynolds HR, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. *Circulation* 2008;**117**:686–697.
3. Tarvasmäki T, Haapio M, Mebazaa A, Sionis A, Silva-Cardoso J, Tolppanen H, Lindholm MG, Pulkki K, Parissis J, Harjola VP, Lassus J. Acute kidney injury in cardiogenic shock: definitions, incidence, haemodynamic alterations, and mortality. *Eur J Heart Fail* 2018;**20**:572–581.
4. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Fuhrmann J, Böhm M, Ebelt H, Schneider S, Schuler G, Werdan K; IABP-SHOCK II Trial Investigators. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 2012;**367**:1287–1296.
5. Champion S. Extracorporeal membrane oxygenation in the therapy of cardiogenic shock (ECMO-CS): the need for a better definition of refractory cardiogenic shock. *Eur J Heart Fail* 2018;**20**:197–198.

6. Hochman JS. Cardiogenic shock complicating acute myocardial infarction: expanding the paradigm. *Circulation* 2003;**107**:2998–3002.
7. Shah M, Patnaik S, Patel B, Ram P, Garg L, Agarwal M, Agrawal S, Arora S, Patel N, Wald J, Jorde UP. Trends in mechanical circulatory support use and hospital mortality among patients with acute myocardial infarction and non-infarction related cardiogenic shock in the United States. *Clin Res Cardiol* 2018;**107**:287–303.
8. Schmidt M, Burrell A, Roberts L, Bailey M, Sheldrake J, Rycus PT, Hodgson C, Scheinkestel C, Cooper DJ, Thiagarajan RR, Brodie D, Pellegrino V, Pilcher D. Predicting survival after ECMO for refractory cardiogenic shock: the survival after veno-arterial-ECMO (SAVE)-score. *Eur Heart J* 2015;**36**:2246–2256.
9. Muller G, Flecher E, Lebreton G, Luyt CE, Trouillet JL, Bréchot N, Schmidt M, Mastroianni C, Chastre J, Leprince P, Anselmi A, Combes A. The ENCOURAGE mortality risk score and analysis of long-term outcomes after VA-ECMO for acute myocardial infarction with cardiogenic shock. *Intensive Care Med* 2016;**42**:370–378.
10. Chen WC, Huang KY, Yao CW, Wu CF, Liang SJ, Li CH, Tu CY, Chen HJ. The modified SAVE score: predicting survival using urgent veno-arterial extracorporeal membrane oxygenation within 24 hours of arrival at the emergency department. *Crit Care* 2016;**20**:336.
11. Harjola VP, Lassus J, Sionis A, Køber L, Tarvasmäki T, Spinar J, Parissis J, Banaszewski M, Silva-Cardoso J, Carubelli V, Di Somma S, Tolppanen H, Zeymer U, Thiele H, Nieminen MS, Mebazaa A; CardShock Study Investigators; GREAT network. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. *Eur J Heart Fail* 2015;**17**:501–509.
12. Harjola VP, Parissis J, Brunner-La Rocca HP, Čelutkienė J, Chioncel O, Collins SP, De Backer D, Filippatos GS, Gayat E, Hill L, Lainscak M, Lassus J, Masip J, Mebazaa A, Miró Ò, Mortara A, Mueller C, Mullens W, Nieminen MS, Rudiger A, Ruschitzka F, Seferovic PM, Sionis A, Vieillard-Baron A, Weinstein JM, de Boer RA, Crespo-Leiro MG, Piepoli M, Riley JP. Comprehensive in-hospital monitoring in acute heart failure: applications for clinical practice and future directions for research. A statement from the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2018;**20**:1081–1099.
13. Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. *Am J Surg* 1996;**171**:221–226.
14. Attaná P, Lazzeri C, Chiostri M, Picariello C, Gensini GF, Valente S. Lactate clearance in cardiogenic shock following ST elevation myocardial infarction: a pilot study. *Acute Card Care* 2012;**14**:20–26.
15. Zhang Z, Xu X. Lactate clearance is a useful biomarker for the prediction of all-cause mortality in critically ill patients: a systematic review and meta-analysis*. *Crit Care Med* 2014;**42**:2118–2125.
16. Allard M, Simonnet G, Dupouy B, Vincent JD. Angiotensin II inactivation process in cultured mouse spinal cord cells. *J Neurochem* 1987;**48**:1553–1559.
17. Prajapati SC, Chauhan SS. Dipeptidyl peptidase III: a multifaceted oligopeptide N-end cutter. *FEBS J* 2011;**278**:3256–3276.
18. Ocaranza MP, Jalil JE. On endogenous angiotensin II antagonism in hypertension: The role of dipeptidyl peptidase III. *Hypertension* 2016;**68**:552–554.
19. Rehfeld L, Funk E, Jha S, Macheroux P, Melander O, Bergmann A. Novel methods for the quantification of dipeptidyl peptidase 3 (DPP3) concentration and activity in human blood samples. *J Appl Lab Med* 2018 https://doi.org/10.1373/jalm.2018.027995.
20. Deniau B, Rehfeld L, Santos K, Dienelt A, Azibani F, Sadoune M, Kounde PR, Samuel JL, Tolpannen H, Lassus J, Harjola VP, Vodovar N, Bergmann A, Hartmann O, Mebazaa A, Blet A. Circulating dipeptidyl peptidase-3 is a myocardial depressant factor: DPP3 inhibition rapidly and sustainably improves hemodynamics. *Eur J Heart Fail* 2019, in press.
21. Levy B, Clere-Jehl R, Legras A, Morichau-Beauchant T, Leone M, Frederique G, Quenot JP, Kimmoun A, Cariou A, Lassus J, Harjola VP, Meziani F, Louis G, Rossignol P, Duarte K, Girerd N, Mebazaa A, Vignon P. Epinephrine versus norepinephrine for cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol* 2018;**72**:173–182.
22. Kohsaka S, Menon V, Lowe AM, Lange M, Dzavik V, Sleeper LA, Hochman JS; SHOCK Investigators. Systemic inflammatory response syndrome after acute myocardial infarction complicated by cardiogenic shock. *Arch Intern Med* 2005;**165**:1643–1650.
23. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, Picard MH, Menegus MA, Boland J, Dzavik V, Thompson CR, Wong SC, Steingart R, Forman R, Aylward PE, Godfrey E, Desvigne-Nickens P, LeJemtel TH. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med* 1999;**341**:625–634.
24. Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, Nordbeck P, Geisler T, Landmesser U, Skurk C, Fach A, Lapp H, Piek JJ, Noc M, Goslar T, Felix SB, Maier LS, Stepinska J, Oldroyd K, Serpytis P, Montalescot G, Barthelemy O, Huber K, Windecker S, Savonitto S, Torremante P, Vrints C, Schneider S, Desch S, Zeymer U; CULPRIT-SHOCK Investigators. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med* 2017;**377**:2419–2432.
25. The TRIUMPH Investigators*, Alexander JH, Reynolds HR, Stebbins AL, Dzavik V, Harrington RA, Van de Werf F, Hochman JS. Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock. *JAMA* 2007;**297**:1657.
26. Reyentovich A, Barghash MH, Hochman JS. Management of refractory cardiogenic shock. *Nat Rev Cardiol* 2016;**13**:481–492.
27. Mebazaa A, Combes A, van Diepen S, Hollinger A, Katz JN, Landoni G, Hajjar LA, Lassus J, Lebreton G, Montalescot G, Park JJ, Price S, Sionis A, Yannopolos D, Harjola VP, Levy B, Thiele H. Management of cardiogenic shock complicating myocardial infarction. *Intensive Care Med* 2018;**44**:760–773.
28. Bassi E, Park M, Azevedo LCP. Therapeutic strategies for high-dose vasopressor-dependent shock. *Crit Care Res Pract* 2013;**2013**:654708.
29. Baran DA, Grines CL, Bailey S, Burkhoff D, Hall SA, Henry TD, Hollenberg SM, Kapur NK, O'Neill W, Ornato JP, Stelling K, Thiele H, van Diepen S, Naidu SS. SCAI clinical expert consensus statement on the classification of cardiogenic shock: this document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. *Catheter Cardiovasc Interv* 2019;**94**:29–37.