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Altered mental status predicts mortality in cardiogenic shock – results from the CardShock study

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Abstract

Background: Altered mental status is among the signs of hypoperfusion in cardiogenic shock, the most severe form of acute heart failure. The aim of this study was to investigate the prevalence of altered mental status, to identify factors associating with it, and to assess the prognostic significance of altered mental status in cardiogenic shock.

Methods: Mental status was assessed at presentation of shock in 215 adult cardiogenic shock patients in a multinational, prospective, observational study. Clinical picture, biochemical variables, and short-term mortality were compared between patients presenting with altered and normal mental status.

Results: Altered mental status was detected in 147 (68%) patients, whereas 68 (32%) patients had normal mental status. Patients with altered mental status were older (68 *vs.* 64 years, p=0.04) and more likely to have an acute coronary syndrome than those with normal mental status (85% *vs.* 74%, p=0.04). Altered mental status was associated with lower systolic blood pressure (76 *vs.* 80 mmHg, p=0.03) and lower arterial pH (7.27 *vs.* 7.35, p<0.001) as well as higher levels of blood lactate (3.4 *vs.* 2.3 mmol/l, p<0.001) and blood glucose (11.4 *vs.* 9.0 mmol/l, p=0.01). Low arterial pH (adjusted odds ratio 1.6 (1.1–2.2), p=0.02) was the only factor independently associated with altered mental status. Ninety-day mortality was significantly higher (51% *vs.* 22%, p<0.001) among patients with altered mental status.

Conclusions: Altered mental status is a common clinical sign of systemic hypoperfusion in cardiogenic shock and is associated with poor outcome. It is also associated with several biochemical findings that reflect inadequate tissue perfusion, of which low arterial pH is independently associated with altered mental status.

Keywords

Cardiogenic shock, acute coronary syndromes, acute heart failure, altered mental status, delirium, acidosis

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Introduction

Cardiogenic shock is the most severe form of acute heart failure, in which cardiac output is insufficient to maintain adequate blood pressure and tissue perfusion. Even with prompt treatment, it often leads to multiorgan failure and death. Mortality rates still approach 40% to 50% despite early revascularization and mechanical support devices.[1] Altered mental status is included in the diagnostic criteria for cardiogenic shock as one of the signs of hypoperfusion.[1,2] Altered mental status is a term used to describe alterations in patients' consciousness and cognition. Overall, critically ill patients often present with symptoms deriving from the central nervous system that vary from mild confusion to delirium and deep coma. Neurological symptoms are detected in up to 70% of septic patients.[3] In addition, critical illness delirium is a well-established phenomenon associated with longer length of stay in the intensive care unit (ICU) and poor outcome.[4,5] Still, neurological symptoms seem to receive little attention in daily clinical practice in cardiology. Moreover, literature regarding cardiac patients is sparse and focuses on the elderly.[6–11] These studies suggest that delirium in acute cardiac patients is associated with increased mortality. However, data on the significance of neurological symptoms among cardiogenic shock patients are lacking. The aim of this study was to investigate the prevalence of altered mental status, to identify patient characteristics associating with it, and to assess the prognostic significance of altered mental status in cardiogenic shock.

Methods

Study population

The CardShock study (NCT01374867 at www.clinicaltrials.gov) is a European multicentre, prospective, observational study conducted between 2010 and 2012. We enrolled consecutive adult cardiogenic shock patients in nine tertiary hospitals within 6 h of the detection of the shock. The detailed study design and main results have been published previously.[12] The inclusion criteria were severe hypotension of acute cardiac cause (systolic blood pressure < 90 mmHg despite adequate fluid resuscitation for at least 30 min or need for vasopressor therapy to maintain systolic blood pressure > 90 mmHg) and signs of hypoperfusion (altered mental status, cold periphery, oliguria (diuresis < 0.5 ml/kg per h for the previous 6 h) or blood lactate > 2 mmol/l). Both acute coronary syndrome (ACS) and non-ACS aetiologies were included. Exclusion criteria were on-going haemodynamically significant cardiac arrhythmia or shock after cardiac surgery. All patients were examined and mental status was assessed clinically by the study physician at the time of enrolment. Altered mental status was defined as somnolence or/and acute mental confusion, agitation or delirium. More exactly, according to common definitions delirium may present as a decline from a previously attained baseline cognition, and is characterized by fluctuating course, disorganized behaviour and loss of orientation or the ability to place oneself correctly by time, location or personal identity. If the patient was sedated and intubated at the time of enrolment, the mental state evaluation was made by the last provided note in the medical record.

Clinical parameters were measured and blood was drawn for biochemical analyses. Creatinine, C-reactive protein, high-sensitivity troponin T (hsTnT) and N-terminal prohormone brain natriuretic peptide (NT-proBNP) (Roche Diagnostics, Basel, Switzerland) were analysed centrally from blood samples stored at –80ºC. Blood leukocytes, haemoglobin, glucose, sodium, lactate and arterial pH were analysed locally. Echocardiography was performed per protocol at study entry. The end-point of interest was 90-day mortality. Informed consent was obtained from the patients or their next of kin. The study was approved by local ethics committees and the investigation conforms to the principles outlined in the *Declaration of Helsinki*.

Statistical analyses

The characteristics and clinical presentation of patients with altered mental status were compared with patients with normal mental status. Categorical variables are presented as numbers (n) and percentages (%), continuous variables as means with standard deviations or medians with interquartile ranges for variables with a skewed distribution. Group comparisons were performed with chi-square test for categorical, and Student's t-test or Mann–Whitney U-test for continuous variables, as appropriate. Univariate- and multivariable regression analyses were performed in order to identify factors associated with altered mental status. Variables with p-value < 0.1 in univariate regression analysis were included in the multivariable model. Results are shown as odds ratios (ORs) with 95% confidence intervals (CIs). The ability of clinical variables to predict altered mental status was assessed by calculating the receiver-operating-characteristics (ROC) area under the curve (AUC). Kaplan–Meier curves were used to illustrate differences in mortality between the groups. The threshold p-value for statistical significance was 0.05. Statistical analyses were performed by SPSS 22.0 statistical software (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

Mental status was recorded at the time of enrolment in 215 cardiogenic shock patients. Altered mental status was detected in 147 (68%) patients, whereas 68 (32%) patients

Table 1. Patient characteristics, medical history and short-term mortality.

	All	Patients with altered mental status	Patients with normal mental status	*p*-value
N (%)	215	147 (68)	68 (32)	
Age; years (SD)	67 (12)	68 (11)	64 (13)	**0.04**
Female	56 (26)	38 (26)	18 (26)	0.9
BMI; kg/m^2	26.9 (4.2)	26.7 (4.2)	27.2 (4.2)	0.5
ACS aetiology	175 (81)	125 (85)	50 (74)	**0.04**
PCI	147 (68)	102 (69)	45 (66)	0.6
Resuscitation	61 (28)	49 (33)	12 (18)	**0.02**
Intubation	133 (63)	109 (75)	24 (37)	**< 0.001**
Receiving opiates (24h)	149 (71)	104 (72)	45 (67)	0.4
Receiving sedatives (24h)	132 (62)	109 (76)	23 (34)	**< 0.001**
Hospital LOS	13 (7–24)	15 (8–27)	11 (5–20)	**0.01**
Medical history				
Coronary artery disease	75 (35)	56 (38)	19 (28)	0.15
Congestive heart failure	35 (16)	22 (15)	13 (19)	0.4
Diabetes mellitus	61 (28)	44 (30)	17 (25)	0.5
Hypertension	130 (60)	93 (63)	37 (54)	0.2
Hyperlipidaemia	99 (46)	69 (47)	30 (44)	0.7
Renal insufficiency	24 (11)	19 (13)	5 (7)	0.2
COPD	18 (8)	14 (10)	4 (6)	0.4
Cerebrovascular disease	22 (10)	14 (10)	8 (12)	0.6
Alcohol abuse	26 (12)	19 (13)	7 (10)	0.6
Smoker	84 (39)	59 (40)	25 (37)	0.6
Mortality				
In-hospital	79 (37)	67 (46)	12 (18)	**< 0.001**
90-day	88 (42)	73 (51)	15 (22)	**< 0.001**

Categorical variables are presented as numbers (%), continuous variables as means (standard deviation) for normally distributed variables and as medians (inter-quartile ranges) for variables with a skewed distribution. *p*-values are for the difference between patients with altered mental status and normal mental status.
ACS: acute coronary syndrome; BMI: body mass index; COPD: chronic obstructive pulmonary disease; LOS: length of stay; PCI: percutaneous coronary intervention.

had normal mental status. Patients with altered mental status were older than those with normal mental status (mean age 68 (11) *vs*. 64 (13) years, $p = 0.04$) and were more likely to have an ACS aetiology of cardiogenic shock (85% *vs*. 74%, $p = 0.04$). The prevalence of altered mental status was higher in ACS patients (72%) compared with non-ACS patients (55%), $p = 0.04$. We found no differences in medical history, gender, alcohol abuse or body mass index between the groups. Altered mental status at the time of enrolment was associated with longer hospital length of stay (15 (8–27) *vs*. 11 (5–20) days, $p = 0.01$). Both intubation (75% *vs*. 37%, $p < 0.001$) and resuscitation (33% *vs*. 18%, $p = 0.01$) were more common among patients with altered mental status, as was administration of sedatives during the first 24 h (76% *vs*. 34%, $p < 0.001$). Patient characteristics are shown in more detail in Table 1.

Clinical presentation and biochemistry

Data on clinical presentation and biochemistry at the time of enrolment are shown in Table 2. Systolic blood pressure (76 (12) *vs*. 80 (16) mmHg, $p = 0.03$) and left ventricular ejection fraction (LVEF) (32% (14) *vs*. 36% (14), $p = 0.05$) were lower in patients with altered mental status compared with those with normal mental status. No differences in heart rate, proportion of patients in sinus rhythm, or prevalence of infection were found between the groups. Arterial pH was significantly lower (7.27 (0.14) *vs*. 7.35 (0.09), $p < 0.001$), while blood lactate (3.4 (2.1–6.6) mmol/l vs. 2.3 (1.5–3.4) mmol/l, $p < 0.001$) and blood glucose levels (11.4 (8.2–17.6) *vs*. 9.0 (7.3-13.4) mmol/l, $p = 0.01$) were higher in patients with altered mental status. We found no differences in the levels of haemoglobin, leukocytes, C-reactive protein, renal function or NT-proBNP between the groups. hsTnT levels tended to be higher in patients with altered mental status.

In univariate logistic regression analysis, age was identified as a risk factor for altered mental status (OR 1.03 (1.001–1.05), $p = 0.04$). ACS aetiology (OR 2.0 (1.01–4.1), $p = 0.05$), lower arterial pH (OR 1.9 (1.4–2.6), $p < 0.001$, for 0.1 decrease in pH), higher blood lactate (OR 1.2 (1.07–1.3), $p = 0.002$) and higher blood glucose (OR 1.05

Table 2. Clinical presentation and biochemistry at the time of enrolment.

Clinical presentation	All	Patients with altered mental status	Patients with normal mental status	*p*-value
Systolic blood pressure; mmHg (SD)	78 (13)	76 (12)	80 (16)	**0.03**
Mean arterial pressure; mmHg	57 (10)	56 (10)	59 (10)	0.06
Left ventricular ejection fraction; %	33 (14)	32 (14)	36 (14)	**0.05**
Heart rate; beats/min	90 (28)	91 (30)	87 (24)	0.3
Sinus rhythm; *n* (%)	156 (73)	108 (74)	48 (72)	0.7
Infection	31 (15)	24 (17)	7 (10)	0.2
Lactate > 2 mmol/l	152 (72)	112 (77)	40 (60)	**0.01**
Cold periphery	203 (95)	142 (97)	61 (91)	0.09
Oliguria	119 (56)	85 (59)	34 (50)	0.2
Biochemistry				
Blood leukocytes; E9/l	14.6 (5.7)	14.7 (6.0)	14.2 (4.8)	0.6
Blood haemoglobin; g/l	128 (22)	129 (23)	128 (21)	0.8
Plasma creatinine; µmol/l	106 (84–141)	112 (85–144)	97 (80–131)	0.08
Plasma sodium; mmol/l	137 (5)	137 (5)	136 (6)	0.5
Plasma glucose; mmol/l	10.7 (7.8–16.0)	11.4 (8.2–17.6)	9.0 (7.3–13.4)	**0.01**
Plasma lactate; mmol/l	2.8 (1.7–5.8)	3.4 (2.1–6.6)	2.3 (1.5–3.4)	**< 0.001**
Arterial pH	7.29 (0.13)	7.27 (0.14)	7.35 (0.09)	**< 0.001**
Plasma NT-proBNP; ng/l	2661 (608–9286)	2475 (590–8904)	3824 (626–9715)	0.7
Plasma hsTnT; ng/L	2260 (398–5380)	2580 (441–5784)	1717 (143–4180)	0.15
Plasma C reactive protein; mg/l	17 (4–53)	15 (4–50)	19 (5–55)	0.4

Numbers are presented as means (standard deviation) for normally distributed variables and as medians (inter-quartile range) for variables with a skewed distribution. Categorical variables are presented as numbers (%). *p*-values are for the difference between patients with altered mental status and normal mental status.
hsTnT: high-sensitivity troponin T; NT-proBNP: N-terminal prohormone brain natriuretic peptide.

Table 3. Multivariable regression analysis for altered mental status.

	Odds ratio	95% CI	*p*-value
Age, per one year increase	1.03	1.00–1.06	0.09
Male gender	1.2	0.53–2.8	0.6
ACS aetiology	1.6	0.67–4.0	0.3
Systolic blood pressure, per 1 mmHg decrease	1.02	0.99–1.04	0.2
LVEF, per 1% decrease	1.02	1.00–1.05	0.07
Plasma lactate, per 1 mmol/l increase	1.06	0.93–1.2	0.4
Arterial pH, per 0.1 decrease	1.6	1.08–2.2	**0.02**
Plasma glucose, per 1 mmol/l increase	1.01	0.96–1.07	0.7
Resuscitation	1.5	0.66–3.4	0.3

ACS: acute coronary syndrome; LVEF: left ventricular ejection fraction.

(1.003–1.11), $p = 0.04$) were likewise associated with altered mental status. In addition to these, gender, systolic blood pressure, LVEF and resuscitation were included in the multivariable model. As a result, decreasing arterial pH was the only factor to retain an independent association with altered mental status in multivariable analysis (Table 3). In ROC analysis, the AUC of arterial pH for prediction of altered mental status was 0.71 (95% CI 0.64–0.78, $p < 0.001$). Only small increases in AUC were achieved by adding age or systolic blood pressure to arterial pH (AUC of 0.72, 95% CI 0.65–0.79, $p < 0.001$, for both bivariate models). AUC of the multivariable model including all variables in Table 3 was 0.74 (95% CI 0.66–0.81, $p < 0.001$).

Altered mental status as a predictor of short-term mortality

Mortality was significantly higher among patients with altered mental status, in-hospital mortality being as high as 46% compared with 18% among patients with normal mental status, $p < 0.001$, and 90-day mortality was 51% and 22%, $p < 0.001$, respectively. The relative risk for in-hospital mortality in patients with altered mental status was thus 2.6 and for 90-day mortality 2.3 compared with those with normal mental status. Kaplan–Meier survival curves are shown in Figure 1. After excluding from the analysis patients resuscitated after cardiac arrest, the differences

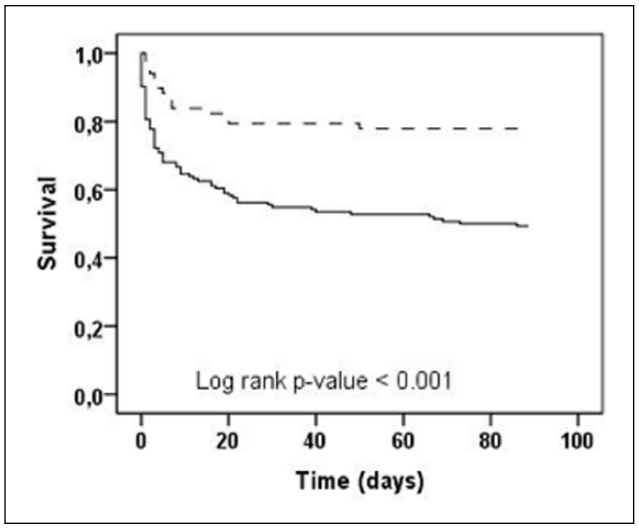

Figure 1. Kaplan–Meier 90-day survival curves for cardiogenic shock patients presenting with altered mental status and normal mental status (dotted line).

remained similar: in-hospital mortality was 40% *vs*. 14% ($p = 0.001$) and 90-day mortality 47% *vs*. 20% ($p = 0.001$) in patients presenting with and without altered mental status, respectively. Moreover, altered mental status was an independent predictor of in-hospital mortality in cardiogenic shock (OR 3.0 (1.1–8.1), $p = 0.03$) when adjusted for age, gender, ACS aetiology, prior coronary artery bypass grafting, previous myocardial infarction, baseline blood lactate, LVEF and systolic blood pressure.[12]

Discussion

The CardShock study is a large, multicentre and multinational study that illustrates the current clinical picture and outcome of cardiogenic shock patients. In this study, we have three main findings. First, altered mental status is a very common symptom and an important sign of systemic hypoperfusion among cardiogenic shock patients. Second, mortality is significantly higher in patients with altered mental status compared with those with normal mental status. Third, while altered mental status is associated with several clinical signs and biochemical findings that reflect tissue hypoperfusion, low arterial pH has the strongest association with altered mental status.

The majority of this cardiogenic shock study population had altered mental status as a sign of significant hypoperfusion at presentation. Actually, the prevalence of altered mental status was very similar to that detected in the IABP-SHOCK II Trial.[13] Moreover, the proportion of cardiogenic shock patients presenting with altered mental status was equal to septic patients, although mechanisms behind the symptoms may differ.[3] Importantly, the reported prevalence of critical illness delirium varies substantially from 20% to over 80% depending on the study population and methods used for screening.[14–17] When structured delirium screening tests (Confusion Assessment Method for ICU or other) are used, less pronounced alterations of mental state (e.g. hypoactive type of delirium) may be underdiagnosed due to negative screening test results.[18] The prevalence of delirium in three previous cardiac ICU patient cohorts was lower (29%, 20% and 19%) than the prevalence of altered mental status in our study population.[6–8] However, those cohorts included the whole spectrum of cardiac patients admitted to an ICU, in contrast to our population with cardiogenic shock as the specific inclusion criteria, and were based on structured delirium screening tests.

Patients with altered mental status were older than those with normal mental status. This is in line with multiple studies that indicate age to be a risk factor for acute brain dysfunction and delirium during critical illness.[19–21] Except for age, the medical history was very similar in both groups, suggesting that previous medical history is not a significant determinant of the development of altered mental status. This is in accordance with the results from a study of general cardiac ICU patients.[6] Interestingly, history of alcohol abuse or cerebrovascular disease were not associated with altered mental status. Indeed, the significance of these potential risk factors for acute brain dysfunction and delirium has remained controversial in previous studies as well.[6,21–24] With regard to management of cardiogenic shock, intubation, resuscitation and administration of sedatives were more common among patients with altered mental status. In fact, symptoms deriving from the central nervous system, including agitation and delirium, may have led to sedation and intubation of the patient.

Of note, ACS aetiology had a positive correlation with altered mental status. This may reflect the sudden onset of haemodynamic derangement in myocardial infarction. These patients suffer from instantaneous impairment of cardiac function and consequent drop in blood pressure. In contrast, patients developing cardiogenic shock due to acute decompensation of chronic congestive heart failure may already have adapted to lower cardiac output. In general, systolic blood pressure was lower among patients with altered mental status compared with patients with normal mental status. Indeed, hypotension impairs cerebral blood flow and may result in neuronal injury and ultimately in haemodynamic stroke.[25] In addition, hypotension may induce ischaemia or hyperaemia of the brain tissue due to dysfunctional cerebral autoregulation, which has been associated with the development of delirium in septic patients.[26,27]

Regarding biochemistry at the time of enrolment, lactate levels were more elevated and arterial pH levels lower in patients with altered mental status compared with those with normal mental status. Hyperlactatemia and acidosis indicate inadequate systemic tissue perfusion and oxygen supply. Several studies have shown that increasing lactate values, even within the normal range, are associated with higher mortality rates.[28,29] In cardiogenic shock, excessive lactate production is the major

contributor to acidosis, and hyperlactatemia is a universal marker of severity of acute illness and a predictor of poor outcome.[28,30] Importantly, our study demonstrates that low arterial pH had the strongest association with altered mental status. Arterial pH remained the only factor independently associated with altered mental status in multivariable regression analysis. Indeed, acidosis is harmful to cerebral tissue through severe neuronal injury and cell death.[31] In addition, metabolic acidosis has been identified as a risk factor for ICU-delirium.[19]

Interestingly, blood glucose level was also significantly higher in patients with altered mental status, although no difference in the prevalence of diabetes mellitus was found between the groups. Higher admission blood glucose has been associated with increased mortality both in cardiogenic shock and acute heart failure.[32,33] Hyperglycaemia is related to the release of stress mediators, such as catecholamines and cortisol, that induce gluconeogenesis and glycolysis.[34] Moreover, hyperglycaemia may also be partly due to hyperlactatemia, since excessive lactate can be converted back to glucose in the liver.

The CardShock study demonstrates that clinically assessed mental status has prognostic significance in cardiogenic shock. Both in-hospital and 90-day mortality were higher among patients with altered mental status compared with those with normal mental status. Interestingly, the prognostic impact of altered mental status on short-term mortality is in line with the results presented in a recent review about critical illness delirium.[4] Clinically evaluated anoxic brain damage in cardiogenic shock patients was also indicated to be a powerful predictor of adverse outcome in the SHOCK Trial and Registry.[35] What our study illustrates, however, is that even milder manifestations of mental state alterations affect the prognosis in cardiogenic shock. Moreover, in contrast to delirium that usually develops only one or more days after hospitalization, clinically evaluated altered mental status indicates a more severe course of cardiogenic shock already at the time of detection of the shock. As a strong and independent risk factor for mortality in cardiogenic shock, altered mental status has also been incorporated as a variable in a recently developed risk score for prediction of in-hospital mortality.[12] Apart from altered mental status, other conventional signs of hypoperfusion have some limitations in clinical practice. In this study, cold periphery was present in almost all of the patients, which makes it a less useful tool when sorting out high-risk and low-risk patients. Furthermore, oliguria requires several hours of follow-up for identification and is most often preceded by other signs of hypoperfusion. Thus, it performs suboptimally for early detection of the shock. This highlights the point that assessment of mental state deserves special attention in the management of cardiogenic shock patients.

Our study has certain limitations. First, mental state was evaluated by the study physician and no structured screening tools were used. However, such scores would underestimate the spectrum of mental state alterations due to hypoperfusion, especially the less conspicuous presentations. Glasgow Coma Scale provides a tool to evaluate the level of consciousness, emphasizing the more severe forms of mental state alterations, for example, after head injury or in sedated patients. Confusion Assessment Method for ICU, in turn, aims to recognize critical illness delirium that is seldom present already at hospital admission. In addition, the objective of this study design was to assess the relevance of a quick, clinically made mental state evaluation. Considering the emergency setting of cardiogenic shock, no time-consuming tests are applied in clinical practice. Second, no information on subsequent progression of mental state was collected. Nevertheless, it is well known that the majority of cardiogenic shock patients are sedated and intubated. Thus, sequential evaluation of mental state was not considered feasible for research purposes.

Conclusions

Altered mental status is a common and easily detectable clinical sign of significant hypoperfusion in cardiogenic shock patients. It is associated with other findings of inadequate tissue perfusion as well as hyperglycaemia. Of those, low arterial pH has the strongest association with altered mental status. More importantly, altered mental status is associated with high short-term mortality in cardiogenic shock. Thus, adequate attention should be paid to close assessment of mental state. As soon as detected, altered mental status calls not only for symptomatic management but also for prompt action to improve organ perfusion.

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Conflict of interest

JL has received speakers fees or/and honoraria from advisory board meetings from Bayer, Boehringer Ingelheim, Novartis, Orion Pharma, Pfizer, Roche Diagnostics, Servier and Vifor Pharma (outside the submitted work). LK has received personal fees as speaker at symposia (outside the submitted work). AS has received personal fees and non-financial support from Orion-Pharma, grants, personal fees and non-financial support from Astra Zeneca, personal fees and non-financial support from Pfizer and Bayer, grants and non-financial support from Menarini, non-financial support from Maquet and Singulex and personal fees from Boehringer (outside the submitted work) . JP has received personal fees outside the submitted work. AM has received personal fees from Novartis, Orion, Roche, Servier, Cardiorentis and Zs Pharma, grants and personal fees from Adrenomed and grants from MyCartis and Critical diagnostics (outside the submitted work). VH has served on advisory boards for Bayer, BMS/Pfizer, Boehringer-Ingelheim, MSD, Roche Diagnostics, Novartis, and Servier, and received lecture fees from Bayer, BMS/Pfizer, Orion

Pharma, Resmed, and Roche Diagnostics (outside the submitted work). All other authors have no conflicts to declare.

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