Added value of serial bio-adrenomedullin measurement in addition to lactate for the prognosis of septic patients admitted to ICU

Alice Blet 1,2, Charles de Roquetaillade 1,2, Oliver Hartmann 3, Joachim Struck 3, Alexandre Mebazaa 1,2, Benjamin Glenn Chousterman 1,2* and on behalf of the AdrenOSS-1 study investigators

To the editor:

Sepsis mortality decreased over the last decades, although it remains dramatically high [1]. The implementation of guidelines such as the Surviving Sepsis Campaign (SSC) contributed to these progresses. SSC recommends to guide resuscitation on normalization of lactate levels [2]. Guiding resuscitation on lactate reduction is highly debated [3]. Anyway, normalization of lactate is associated with improved outcome [4]. We have recently shown that plasma levels of bio-adrenomedullin (bio-ADM), a peptide regulating vascular integrity and endothelial function, were associated with patient outcome during sepsis [5]. Interestingly, we observed that patients with elevated bio-ADM levels at admission and with low bio-ADM levels 2 days later had similar outcome to patients with persistently low bio-ADM levels. We therefore aimed to evaluate the added value of bio-ADM to lactate measurement in the AdrenOSS-1 cohort.

The AdrenOSS-1 study is a prospective observational study conducted in 24 centers within 5 European countries and included 583 septic patients from June 2015 to May 2016 [5]. The primary endpoint was 28-day mortality. We evaluated the relationship between the association of initial evolution of lactate plasma levels and bio-ADM level at 24 h and outcome in patients for whom both markers were available at admission and 1 day later (“24 h”). As described previously, bio-ADM levels below or above 70 pg/mL were considered respectively as low and high [5].

In patients with high lactate levels (> 2 mmol/L) at admission (n = 328) (Table 1), lactate normalization (< 2 mmol/L) at 24 h was associated with better outcome than in patients with persistently high lactate at 24 h (28-day mortality 15.9% vs 41.9% respectively, HR 3.3 [2.0–5.3], p < 0.001) (Fig. 1). Interestingly, among patients with decreasing lactate, high and low bio-ADM levels at 24 h identified patients with substantially different outcomes (28-day mortality 7% vs 26% for low vs high bio-ADM respectively, HR 4.4 [1.6–11.7], p < 0.005) (Fig. 1). High and low bio-ADM levels at 24 h also differentiated outcome of patients with persistently elevated lactate (HR 4.5 [1.6–12.3], p < 0.005).

In patients with low initial lactate (n = 234 admitted and n = 171 alive at 24 h), overall 28-day mortality was 11.2%, neither lactate nor bio-ADM added prognostic value.

For all analyses, similar results were obtained, when missing 24 h data were replaced by the last available values.

Accordingly, our data suggest that measurement of bio-ADM in addition to lactate may help physicians to refine risk stratification and therefore to guide resuscitation during sepsis.
### Table 1: Clinical characteristics of septic patients admitted with a lactate level > 2 mmol/L and alive at 24 h (n = 269)

| Patient characteristics | All (n = 269) | 24 h lactate < 2 mmol/L and bio-ADM < 70 pg/mL | 24 h lactate < 2 mmol/L and bio-ADM > 70 pg/mL | 24 h lactate > 2 mmol/L and bio-ADM < 70 pg/mL | 24 h lactate > 2 mmol/L and bio-ADM > 70 pg/mL | p value | Number of patients (if not indicated n = 269) |
|-------------------------|--------------|----------------------------------------------|----------------------------------------------|-----------------------------------------------|-----------------------------------------------|--------|-------------------------------------------|
| Number of patients (n, %) | 269 (100)   | 75 (27.9)                                    | 70 (26.0)                                   | 28 (10.4)                                    | 96 (35.7)                                    |        |                                            |
| bio-ADM at admission (pg/ml) | 113.7 [59.3–206.4] | 46.7 [33.1–63.0]                          | 137.3 [103.2–217.8]                        | 61.5 [36.3–84.3]                            | 192.4 [129.0–355.6]                          | < 0.0001 |                                            |
| Lactate at admission (mmol/l) | 3.6 [2.6–5.5]  | 2.8 [2.3–3.5]                               | 3.3 [2.5–4.5]                              | 3.5 [2.7–4.6]                               | 5.4 [3.5–8.8]                               | < 0.0001 |                                            |
| Age (years) | 65.7 [54.7–75.6] | 64.0 [54.4–71.8]                          | 65.7 [58.5–74.3]                           | 66.7 [65.8–76.9]                            | 67.8 [54.6–77.4]                            | 0.4697  |                                            |
| Male sex (n, %) | 171 (63.6)   | 52 (69.3)                                    | 45 (64.3)                                   | 18 (64.3)                                    | 56 (58.3)                                    | 0.5253  |                                            |
| Body mass index (kg/m²) | 26.1 [23.1–30.8] | 26.1 [23.9–29.4]                          | 25.1 [20.5–30.4]                           | 26.4 [22.9–31.3]                            | 27.3 [23.6–31.8]                            | 0.3834  | n = 232                                    |
| Septic shock at admission (n, %) | 172 (63.9)   | 34 (45.3)                                    | 46 (65.7)                                   | 15 (53.6)                                    | 77 (80.2)                                    | 0.0001  |                                            |
| Type of ICU admission |                         |                                             |                                             |                                              |                                              |        | 0.1378                                    |
| Medical (n, %) | 198 (73.6)   | 62 (82.7)                                    | 49 (70.0)                                   | 24 (85.7)                                    | 63 (65.6)                                    |        |                                            |
| Surgical—emergency procedure (n, %) | 60 (22.3)   | 10 (13.3)                                    | 18 (25.7)                                   | 4 (14.3)                                     | 28 (29.2)                                    |        |                                            |
| Surgical—elective procedure (n, %) | 11 (4.1)   | 3 (4.0)                                      | 3 (4.3)                                     | 0 (0.0)                                      | 5 (5.2)                                      |        |                                            |
| Origin of sepsis |                         |                                             |                                             |                                              |                                              | 0.0156  |                                            |
| Lung (n, %) | 87 (32.3)     | 28 (37.3)                                    | 16 (22.9)                                   | 15 (53.6)                                    | 28 (29.2)                                    |        |                                            |
| Bloodstream (n, %) | 35 (13)        | 14 (18.7)                                    | 8 (11.4)                                    | 4 (14.3)                                     | 9 (9.4)                                      |        |                                            |
| Urinary tract (n, %) | 46 (17.1)     | 4 (5.3)                                      | 15 (21.4)                                   | 4 (14.3)                                     | 23 (24)                                      |        |                                            |
| Catheter (n, %) | 15 (5.6)     | 4 (5.3)                                      | 3 (4.3)                                     | 3 (10.7)                                     | 5 (5.2)                                      |        |                                            |
| Peritonitis (n, %) | 16 (5.9)     | 6 (8.0)                                      | 3 (4.3)                                     | 0 (0.0)                                      | 7 (7.3)                                      |        |                                            |
| Endocarditis (n, %) | 14 (5.2)     | 4 (5.3)                                      | 4 (5.7)                                     | 1 (3.6)                                      | 5 (5.2)                                      |        |                                            |
| Bile duct infection (n, %) | 4 (1.5)     | 0 (0.0)                                      | 2 (2.9)                                     | 0 (0.0)                                      | 2 (2.1)                                      |        |                                            |
| CNS (n, %) | 1 (0.4)       | 1 (1.3)                                      | 0 (0.0)                                     | 0 (0.0)                                      | 0 (0.0)                                      |        |                                            |
| Skin and soft tissue (n, %) | 4 (1.5)     | 4 (5.3)                                      | 0 (0.0)                                     | 0 (0.0)                                      | 0 (0.0)                                      |        |                                            |
| Gynecologic (n, %) | 1 (0.4)       | 0 (0.0)                                      | 0 (0.0)                                     | 0 (0.0)                                      | 1 (1.0)                                      |        |                                            |
| Other (n, %) | 46 (17.1)   | 10 (13.3)                                    | 19 (27.1)                                   | 1 (3.6)                                      | 16 (16.7)                                    |        |                                            |
| Medical history |                         |                                             |                                             |                                              |                                              |        | 0.0481                                    |
| Any cardiac comorbidity (n, %) | 184 (68.4)   | 43 (57.3)                                    | 49 (70)                                     | 18 (64.3)                                    | 74 (77.1)                                    | < 0.0001 |                                            |
| Chronic heart failure (n, %) | 29 (10.9)     | 6 (8.0)                                      | 5 (7.2)                                     | 3 (11.1)                                     | 15 (15.8)                                    | 0.2684  |                                            |
| Hypertension (n, %) | 143 (53.8)   | 33 (44.0)                                    | 38 (55.1)                                   | 14 (50.0)                                    | 58 (61.7)                                    | 0.1407  |                                            |
| Diabetes mellitus (n, %) | 76 (28.4)     | 21 (28.0)                                    | 19 (27.5)                                   | 3 (10.7)                                     | 33 (34.4)                                    | 0.1102  |                                            |
| Any noncardiac comorbidity (n, %) | 198 (73.6)   | 51 (68.0)                                    | 55 (78.6)                                   | 21 (75.0)                                    | 71 (74.0)                                    | 0.5447  |                                            |
| Chronic renal disease (n, %) | 31 (11.7)     | 6 (8.1)                                      | 10 (14.5)                                   | 2 (7.1)                                      | 13 (13.7)                                    | 0.4978  |                                            |
| Active/Recent malignant tumors (n, %) | 60 (22.5)   | 10 (13.3)                                    | 19 (27.9)                                   | 7 (25.0)                                     | 24 (25.0)                                    | 0.1565  |                                            |
| Smoking (active) (n, %) | 57 (21.8)     | 17 (23.0)                                    | 15 (22.1)                                   | 5 (19.2)                                     | 20 (21.5)                                    | 0.9827  |                                            |
| COPD (n, %) | 35 (13.1)   | 9 (12.0)                                      | 12 (17.4)                                   | 5 (17.9)                                     | 9 (9.5)                                      | 0.4156  |                                            |
| Table 1  | Clinical characteristics of septic patients admitted with a lactate level > 2 mmol/L and alive at 24 h (n = 269) (Continued) |
|---------|----------------------------------------------------------------------------------------------------------------------|
| Patient characteristics | All | 24 h lactate < 2 mmol/L and bio-ADM < 70 pg/mL | 24 h lactate < 2 mmol/L and bio-ADM > 70 pg/mL | 24 h lactate > 2 mmol/L and bio-ADM < 70 pg/mL | 24 h lactate > 2 mmol/L and bio-ADM > 70 pg/mL | p value | Number of patients (if not indicated n = 269) |
| Any chronic medication (n, %) | 176 (65.4) | 42 (56.0) | 53 (75.7) | 16 (57.1) | 65 (67.7) | 0.0032 | |
| Immunosuppressive therapy (n, %) | 26 (9.7) | 5 (6.7) | 5 (7.1) | 3 (10.7) | 13 (13.9) | 0.3963 | |
| Physiological values at admission | | | | | | | |
| Temperature (°C) | 37.2 [36.3–38.3] | 37.2 [36.4–38.3] | 37.2 [36.4–38.2] | 36.9 [35.8–37.7] | 37.2 [36.3–38.4] | 0.6926 | |
| Mean blood pressure (mmHg) | 73 [62–92] | 82 [68.5–99] | 70.5 [60–64] | 77.5 [58–94.2] | 69 [58.5–86] | 0.0009 | n = 266 |
| Heart rate (beats/min) | 108 [96–122] | 110 [93–123.5] | 107 [95.2–118.7] | 106 [97.7–115] | 112.5 [97.7–130.2] | 0.2976 | |
| Central venous pressure (mmHg) | 8 [5–12] | 8 [5–13] | 7 [3–11] | 8 [7–8] | 9 [6–12] | 0.3535 | n = 75 |
| Glasgow Coma Scale score (points) | 15 [13–15] | 15 [14–15] | 15 [14–15] | 14 [13–15] | 15 [13–15] | 0.4721 | n = 253 |
| Fluid balance (mL) | 2500 [1141–4716] | 1930 [892–2626] | 2156 [1375–3939] | 2820 [1292–4323] | 3657 [1426–5750] | 0.0002 | n = 235 |
| Urine output for 24 h (mL) | 1000 [554–1867] | 1350 [941–2667] | 675 [301–1619] | 1562.5 [951–2220] | 600 [177–1480] | <0.0001 | n = 248 |
| PaO2/FiO2 | 220 [131–330] | 254 [155–362] | 231 [148–321] | 211 [96–330] | 190 [115–314] | 0.1637 | n = 244 |
| Laboratory values at admission | | | | | | | |
| Arterial pH | 7.36 [7.27–7.42] | 7.41 [7.34–7.45] | 7.37 [7.26–7.42] | 7.38 [7.31–7.44] | 7.31 [7.22–7.38] | <0.0001 | n = 261 |
| Bilirubin (µmol/L) | 12 [7–22] | 13 [5.75–22.2] | 11 [5.5–20.5] | 12 [8–20.5] | 12 [7–22] | 0.7229 | n = 259 |
| Platelets (10^9/L) | 188 [116–265] | 180 [128–261] | 176 [110–284] | 243 [135–336] | 181 [110–245] | 0.2770 | n = 268 |
| Creatinine (mg/dL) | 15 [10.2–22.6] | 11.3 [8.5–16.8] | 1.7 [1.23–2.65] | 1.03 [0.74–1.45] | 1.72 [1.2–2.62] | <0.0001 | |
| Urea (mg/dL) | 66 [41–109.91] | 50.45 [36.04–78.34] | 85.29 [53.6–118.77] | 52 [33.48–77.27] | 73.57 [46.7–120.84] | 0.0001 | |
| Hematocrit (%) | 35 [30–39] | 36 [30–39] | 35 [30–40] | 35 [31–37] | 34 [29–40] | 0.9579 | n = 265 |
| White blood cell count (per µm³) | 11,690 [8037–18,142] | 13,400 [8390–18,700] | 11,115 [5497–16,500] | 11,770 [7780–15,950] | 10,780 [4200–17,722] | 0.1827 | n = 268 |
| Troponin T, maximum at admission (ng/mL) | 41.73 [18–219] | 24 [14–50.5] | 40.86 [19.5–126.75] | 14 [13–47] | 87.5 [27.82–329.25] | 0.0515 | n = 73 |
| Troponin I, maximum at admission (ng/mL) | 100 [29.9–323] | 79 [19.25–327.23] | 135 [37.02–233.68] | 114.95 [22.48–230] | 100 [31.9–312.95] | 0.9752 | n = 77 |
| PCT, maximum at admission (ng/mL) | 19.17 [6.39–73.93] | 10.36 [4.35–37.93] | 27.62 [7.75–60] | 54.22 [24.1–112.1] | 43.64 [9.6–1034.1] | 0.0054 | n = 144 |
| PCT, central laboratory (ng/mL) | 15.34 [5.37–48.43] | 8.21 [2.4–18.21] | 22.55 [6.68–53.25] | 7.12 [2.04–20.73] | 29.22 [8.73–648] | <0.0001 | n = 269 |
| BNP, maximum at admission (pg/mL) | 376.2 [159–1132] | 376.2 [169.5–1011] | 356.1 [228–540.2] | 219 [143.7–324] | 757 [141.7–1619.5] | 0.4335 | n = 49 |
| NT-proBNP, maximum at admission (pg/mL) | 5119 [1620–17,118] | 1847 [621–6709] | 3873 [2594–23,052] | 792 [249–3074] | 7097 [4884–24,340] | 0.0135 | n = 54 |
| Organ support at admission | | | | | | | |
| Mechanical ventilation | 125 (46.5) | 24 (32.0) | 29 (41.4) | 12 (42.9) | 60 (62.5) | 0.0008 | |
| Noninvasive (n, %) | 49 (18.2) | 16 (21.3) | 9 (12.9) | 7 (25.0) | 17 (17.7) | | |
| None (n, %) | 95 (35.3) | 35 (46.7) | 32 (45.7) | 9 (32.1) | 19 (19.8) | | |
| Renal replacement therapy (n, %) | 28 (10.4) | 1 (1.3) | 7 (10.0) | 3 (10.7) | 17 (17.7) | 0.0070 | |
| Vasopressors/inotropes at admission (n, %) | 192 (71.4) | 41 (54.7) | 51 (72.9) | 18 (64.3) | 82 (85.4) | 0.0001 | |
| Patient characteristics | All | 24 h lactate < 2 mmol/L and bio-ADM < 70 pg/mL | 24 h lactate < 2 mmol/L and bio-ADM > 70 pg/mL | 24 h lactate > 2 mmol/L and bio-ADM < 70 pg/mL | 24 h lactate > 2 mmol/L and bio-ADM > 70 pg/mL | p value | Number of patients (if not indicated n = 269) |
|-------------------------|-----|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|--------|--------------------------------------------|
| **ICU scoring systems**  |     |                                            |                                            |                                            |                                            |        |                                            |
| SOFA (points)           | 8 [6–11] | 6 [4–9]                                      | 8 [7–11]                                    | 8 [5–9]                                    | 10 [7–11.5]                                | < 0.0001 | n = 240                                    |
| APACHE II (points)      | 17 [13–22] | 15 [10–18]                                   | 17 [12.2–21]                                | 18.5 [13.7–23]                             | 19 [15–23.2]                               | < 0.0001 |                                            |
| ICU length of stay (days)| 6 [3–11] | 5 [3–7.5]                                    | 7 [4–13]                                    | 5.5 [2.7–9.5]                              | 7 [3–16.2]                                 | 0.0170  |                                            |
| **Mortality**           |     |                                            |                                            |                                            |                                            |        |                                            |
| 28-day, deaths (n, %)   | 75 (27.9) | 5 (6.7)                                      | 18 (25.7)                                   | 4 (14.3)                                   | 48 (50.0)                                  | < 0.0001 |                                            |
| 90-day, deaths (n, %)   | 93 (34.6) | 10 (13.3)                                    | 22 (31.4)                                   | 6 (21.4)                                   | 55 (57.3)                                  | < 0.0001 |                                            |

Data are presented as median [IQR] or n (%).
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Listing of site investigators of the AdrenOSS-1 study:

Belgium, Brussels: Pierre-François Laterre, Caroline Berge, Marie-France Dujardin, Suzanne Renard, Xavier Witteboele, Christine Colienne, Diego Castañares Zapatero; Ottignies: Thierry Dugernier, Marco Vinetti, Nicolas de Schynvy, Anne-Thiilays, Jacques Mairesse; Haute-Brabant: Vincent Huberlant, Hélène Pétre, Isabelle Buelens, Pierre-Henri, Hugues Time, Yves Laurent, Loïc Sébastien, Paul Goukens, Laurent Kehr; France, Limoges: Bruno François, Philippe Vigneron, Nicolas Pichon, Emmanuelle Begoet, Anne-Laure Fedou, Catherine Chapellas, Antoine Galy, Nicolas Rodier, Ludmilla Baudrillard, Michelle Nouaille, Séverine Lalou, Claire Mancia, Thomas Daix, Paul Bourzeix, Isabelle Héra, Anne-Aurore Duchambon; La Rochelle: Jean Baptiste Lascarrou, Maud Fiancette, Gwenhaël Colin, Matthieu Levy-Lagage, Christopher Leber, Laurent Martin-Lev-Lerne, Isabelle Vritier, Alain Yehia, Konstantinos Bachoumas, Aurélie Joret, Jean Reigner, Cécile Rousseau, Nathalie Marquignou, Yolande Alcout, Vanessa Erragne Zinzonni, Angélique Deschamps, Angelina Robert; Tours: Emmanuelle Mercier, Véronique Simeon-Veleles, Aurélie Aubrey, Christine Malatit, Denis Garot, Stephan Ehrmann, Annick Legras, Manikandan, Yousouf Jouan, Pierre-François Dequin, Antoine Guillot, Aëtia Béchet-Contentin, Emmanuelle Roux, Charlotte Salmon, Lysiane Brice, Stéphane Massat, Angoulême: Arnaud Desachy, Marie Anne Fally, Laurence Robin, Christophe Caccio, Charles Lafort, Sylvie Calvat, Stéphane Rouleau, David Schnell, Angers: Sigismund Lasocki, Philippe Fesard, Damien Leblanc, Guillaume Bouhours, Claire Chassier, Mathieu Conte, Thomas Gaillard, Floriane Denou, Mathieu Kervyn, Marion Guyon, Anthéa Loiz, Stéphanie Lebreton; Strasbourg – Nouvel Hôpital Civil: Pierre Meziani, Hatay Allam, Samir Charnaf, Hassène Rahmani, Sarah Heenen, Christine Kumermer, Xavier Delabranche, Alexandre Boivin, Raphaël Clerc-Jehl, Yannick Rabouel; Strasbourg – Hôpital Haute-Pierre: Julien Poit, Sophie Bayer, Catherine Metzger, Stéphane Heckettsweiler, Pierre Olivier Ludes, Hortense Benacencourt, Nadia Dhi, Guy Frey, Jean-Marc Lessinger, Anne Leunoy, Aude Ruym, Alain Meyer, M. Sazagot; Paris – Hôpital Lariboisière: Alexandre Mebazaa, Nicolas De, Etienne Gayat, Marie-Céline Fournier, Sarra Aboug, Badr Louda, Elodie Feliot, Sébastien Voicu, Isabelle Malinson, Bruno Megarbane, Philippe Manivet, Gardiance Vici, Da Silva Kelly, Béatrice La Fouchet, Valérie Pierre, Lamia Kerdjia, Thomas Bee, Antoine Gouay, Pierre Garcon, Samuel Guiguen, Benjamin Glenn Chousterman, Benjamin Huot, Romain Barthelem, Benjamin Sayay, Paris – Hôpital St Louis: Laurent Jacob, Mathieu Legrand, Marie-Céline Fournier, Francine Bonnet, Chloé Legall, Haikel Oueslati, Alexandre Cupacu, Philippe Manivet, Badr Louda, Paris – Hôpital Bichat: Romain Sonneville, Sophie Letrou, Lilou Bryadma, Bruno Mourvillier, Véronique Deier, Eric Magalhaes, Mathilde Neville, Jean-François Timion, Agnès Rejou; Colombe: Stéphane Gaudry, Emeline Dubief, Jonathan Messika, Béatrice La Combe, Damien Roux, Guillaume Berquier, Mohamed Laisi, Jean-Damien Ricard, Clemont Fennard, Jean-Michel Constanti, Sébastien Perret, Julie Delmas, Julien Pascal, Sophie Cayot, Renaud Guerin, Matthieu Jabaudon, Laurence Roszyk, Christine Rolhion, Justine Boudier, Mathilde Lematte, Charline Gouhé, Camille Verhac, Thomas Godet, Sophieh Schnad, Etoile Caumon, Sandrine Thibault, Germany: Aachen: Matthias Lehm, Tobias Schuerholz, Jessica Pezechka, Florian Feld, Christian Brüll, Thorben Beecher, Tim-Philipp Simon, Robert Deisz, Achim Schindler, Bianca Meier, Thorsten Jansch, Köln: Andreas Hohn, Dirk Schedler, Wolfgang Witsh, Daniel Schröder; Erfurt: Andreas Meier-Heßmann, Alexander Lucht, Robert Henker, Magdalena Römmer, Torsten Meinig; Frankfurt: Kai D. Zacharowski.

Fig. 1 Impact of 24 h lactate and bio-ADM values in patients with elevated lactate level at admission. The green curve in the left KM-plot illustrates data from 75 patients with 5 events, the red curve 70 patients with 18 events. The green curve in the right KM-plot illustrates data from 28 patients with 4 events, the red curve 96 patients with 48 events. Of note, differences in numbers between admission (n = 328) and 24 h (n = 269) is related to initial mortality.
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Availability of data and materials
AM had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval and consent to participate
The present study was conducted in France, Belgium, The Netherlands, Italy, and Germany. The study protocol was approved by the local ethics committees, and the study was conducted in accordance with Directive 2001/20/EC as well as good clinical practice (International Conference on Harmonization Harmonized Tripartite Guideline version 4 of May 1, 1996, and decision of November 24, 2006) and the Declaration of Helsinki. Patients were included from June 2015 to May 2016.

Consent for publication
Not applicable.

Competing interests
AM has received speaker’s honoraria from Novartis, Orion, and Servier and fees as a member of the advisory board and/or steering committee from Cardiorentis, Adrenomed, sphingotec, Sanofi, Roche, Abbott, and Bristol-Myers Squibb. EG has received consulting fees from Adrenomed, Roche Diagnostics, and Magnisense and lecture fees from Edwards Lifesciences. OH and JS are employees of sphingotec GmbH, the company that developed and holds patent rights in the bio-ADM assay. BC received fees as a member of an advisory board from Roche Diagnostics. The other authors declare that there are no competing interests.

Author details
1Department of Anesthesiology and Critical Care, Hôpital Lariboisière, DMU Parabol, APHP.Nord, Paris, France. 2Inserm U942 MASCOT, Université de Paris, Paris, France. 3Sphingotec GmbH, Hennigsdorf, Germany.

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