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Hemodynamic Response to Crystalloids or Colloids in Shock: An Exploratory Subgroup Analysis of the CRISTAL Trial.

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3 **1 Hemodynamic Response to Crystalloids or Colloids in Shock: An Exploratory**
4 **2 Subgroup Analysis of the CRISTAL Trial.**
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36 **Keywords:** Fluid resuscitation; Crystalloid; Colloid; Pulmonary artery catheter;

37 **Intensive Care Unit (ICU).**

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2
3 47 **Abstract**
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11 Objective: To compare the hemodynamic effect of crystalloids and colloids during
12 acute severe hypovolemic shock.
13

14 Design: Exploratory subgroup analysis of a multicenter randomized controlled trial
15 (CRISTAL, ClinicalTrials.gov NCT00318942).
16

17 Setting: CRISTAL was conducted in ICUs in Europe, North Africa, and Canada.
18

19 Participants: Current analysis included all patients who had a pulmonary artery
20 catheter in place at randomisation. 220 patients (117 received crystalloids vs. 103
21 colloids) underwent pulmonary artery catheterization.
22

23 Intervention: Crystalloids versus colloids for fluid resuscitation in hypovolemic shock.
24

25 Outcome measures: Hemodynamic data were collected at the time of randomization
26 and subsequently on days 1, 2, 3, 4, 5, 6, 7.
27

28 Results: Median cumulative volume of fluid administered during the first 7 days was
29 higher in the crystalloids group than in the colloids group (3500 [2000 ;6000] vs. 2500
30 [1000 ;4000] ml, $P = .01$). Patients in the colloids arm exhibited a lower heart rate
31 over time compared to those allocated to the crystalloids arm ($P = .014$). There was
32 no significant difference in cardiac index ($P = .053$), mean blood pressure ($P = .4$),
33 arterial lactates ($P = .9$) or global SOFA score ($P = .3$) over time between arms.
34

35 Conclusions: In the CRISTAL trial, patients monitored by a pulmonary artery catheter
36 achieved broadly similar hemodynamic goals, using lower volumes of colloids than
37 crystalloids. The heart rate was lower in the colloids arm.
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70 Strengths and limitations of this study

- 71 • Subgroup analysis of a large international multicenter trial (CRISTAL).
- 72 • CRISTAL was a pragmatic, open label trial.
- 73 • The main focus was to compare the hemodynamic effect of crystalloids vs.
74 colloids in patients monitored by pulmonary artery catheter during acute
75 severe hypovolemic shock.
- 76 • Some data are missing, since hemodynamic variables were not part of the
77 outcomes measured during the CRISTAL trial.

78

79 Introduction

80

81 Fluid resuscitation is a cornerstone of the management of hypovolemia.¹ During
82 hypovolemic shock, administered fluids restore intravascular volume, cardiac output,
83 oxygen delivery and reverse peripheral hypoperfusion.² Resuscitation fluids are
84 divided into two distinct categories, crystalloids and colloids.³ On the one hand,
85 crystalloids dilute the plasma protein content, reducing the oncotic pressure of
86 plasma which may result in interstitial oedema. The most commonly used crystalloid,
87 isotonic saline, induces hyperchloremic acidosis when administered in large
88 quantities.^{4 5} Liberal chloride administration may also be associated with an
89 increased risk of acute kidney injury.⁶ On the other hand, colloids are composed of
90 large molecules, which have difficulty crossing the endothelium and are theoretically
91 more effective for fluid resuscitation.^{7 8} However, the most commonly used family of
92 colloids, starch, exhibits undesirable effects including acute kidney injury and an
93 increased need for renal replacement therapy as well as accumulation in
94 reticuloendothelial tissues, and a negative effect on bleeding and increased
95 requirement for blood products.⁹⁻¹¹ A series of large clinical trials were recently
96 undertaken aiming at determining which fluid was superior for the resuscitation of
97 critically ill patients.¹²⁻¹⁶

98 The CRISTAL trial addressed the issue using a pragmatic approach; rather than
99 studying one fluid versus another, both categories of fluids, crystalloids and colloids
100 were compared as a treatment of acute severe hypovolemia.¹⁷ The CRISTAL trial
101 included 2857 subjects treated in 57 intensive care units (ICU). The primary outcome,
102 28 day mortality, did not significantly differ, with 25.4% mortality in the colloids arm
103 vs. 27% in the crystalloids arm. This finding was similar to results from previous large

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3 104 trials comparing a single colloid to a single crystalloid.¹³⁻¹⁵ However, mortality by 90
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5 105 days was significantly lower in the colloids arm than in the crystalloids arm (30.7% vs.
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7 106 34.2%). This finding was deemed exploratory. Additionally, the number of days alive
8
9 107 at 7 and 28 days without vasopressor therapy was higher in the colloids than in the
10
11 108 crystalloids arm. We sought to compare the effect of crystalloids to that of colloids on
12
13 109 hemodynamic parameters during hypovolemic shock. The pulmonary artery catheter
14
15 110 (PAC) remains the only method to provide a comprehensive, reliable and
16
17 111 reproducible measure of hemodynamic data. Contrary to other methods, the PAC
18
19 112 can determine pulmonary artery pressures, pulmonary artery occlusion pressure as
20
21 113 well as derived variables.¹⁸ The current study is aimed at assessing the
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23 114 hemodynamic effect of crystalloids or colloids in the group of patients monitored by
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25 115 pulmonary artery catheter.
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117 **Materials and Methods**

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119 1) Study setting and patients

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121 The current study is a subgroup analysis of a randomized multicentre trial (CRISTAL,
122 ClinicalTrials.gov NCT00318942), comparing the effect of crystalloid vs. colloid
123 administration for fluid resuscitation in the intensive care unit on mortality at 28 days.

124 ¹⁷ CRISTAL was a non-blinded, pragmatic study. Included subjects required fluid
125 resuscitation for hypovolemia and were randomized to receive either crystalloids or
126 colloids. Crystalloids consisted of isotonic or hypertonic saline as well as buffered
127 solutions, while colloids comprised albumin, gelatins, dextrans and hydroxyethyl
128 starches. Patients were managed throughout their stay in the ICU with the same fluid
129 category. The type of fluid within the assigned group as well as the amount of fluid to
130 be administered was determined by the investigator in charge of the patient. The
131 study protocol was approved by local institutional review boards. Deferred informed
132 consent was obtained from participants or legally authorized surrogates.

133 For the current ancillary study, among the CRISTAL population, we included all
134 patients who had a PAC in place as part of their routine management either prior to
135 or within the first 24 hours of randomization.

136

137 2) Data collection

138 Demographic and general characteristics

139 The following data were prospectively collected at the time of randomization: age,
140 gender, weight, source of admission, McCabe class ¹⁹ and disability scale score. ²⁰
141 Severity scores included the Glasgow coma score, ²¹ Simplified Acute Physiology
142 Score II (SAPS II) ²² and the Sequential Organ Failure Assessment (SOFA) Score. ²³

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3 143 Causes of acute hypovolemia including sepsis, trauma and other disorders were
4
5 144 recorded. We collected a set of symptoms of acute hypovolemia (see supplemental
6
7 145 table 1).
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10 146 Hemodynamic variables

11 147 We prospectively measured as long as the PAC was in place or up to seven days
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13 148 (pending which occurred first), at baseline and once daily (i.e. the first value reported
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15 149 in the medical file following the change of shift, typically around 08h00) heart rate
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17 150 (HR, bpm), systolic (SBP, mmHg), diastolic (DBP, mmHg) and mean blood (MBP,
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19 151 mmHg) pressure, central venous pressure (CVP, mmHg), systolic (PSBP, mmHg),
20
21 152 diastolic (PDBP, mmHg) and mean pulmonary artery (PMBP, mmHg) pressure,
22
23 153 pulmonary artery occlusion pressure (PAOP, mmHg), cardiac index ($L/min/m^2$), and
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25 154 urinary output ($ml/kg/hour$). We calculated, using standard formulas, the product of
26
27 155 heart rate and systolic blood pressure (or rate-pressure product, RPP), a marker of
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29 156 myocardial perfusion requirement, and systemic (SVR, $dyn.s/cm^5$) and pulmonary
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31 157 (PVR, $dyn.s/cm^5$) vascular resistances, stroke volume index (SVI, ml/m^2), left
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33 158 (LVSWI, $g.m/m^2$) and right (RVSWI, $g.m/m^2$) ventricular stroke work index. Laboratory
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35 159 values included arterial pH, levels of bicarbonate ($mmol/l$), lactate ($mmol/l$) and SvO_2
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43 161 Additionally, in order to compare colloids to crystalloids in achieving the
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45 162 hemodynamic targets of the 6-hour bundles of the Surviving Sepsis campaign, we
46
47 163 collected these same variables, six hours after randomisation.²⁴
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51 165 Other variables

52 166 We collected at baseline and daily up to seven days post randomization, the SOFA
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54 167 score and main interventions including the cumulative volume of administered fluids,
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3 168 blood products transfusion, type and dose of vasopressors, mechanical ventilation,
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5 169 and renal replacement therapy.
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10 171 3) Statistical analysis

11 172 Quantitative variables are expressed as median [interquartile range] and categorical
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13 173 variables as number (percentage). The time course over a 7 day period of mean,
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15 174 systolic and diastolic blood pressure, central venous pressure, heart rate, cardiac
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17 175 index, results of arterial blood gases and daily diuresis were compared between
18
19 176 arms. We then compared systolic, diastolic and mean pulmonary artery pressure and
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21 177 pulmonary artery occlusion pressure in both arms. In order to further explore
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23 178 differences between both arms, we calculated the rate pressure product as well as
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25 179 the various indexes derived from the use of the PAC and compared them between
26
27 180 arms. Mixed effects models, which are appropriate for clustered and dependent data,
28
29 181 were used to study the relationship between treatment arms and the time course of
30
31 182 hemodynamic variables as well as the global SOFA score.²⁵ The area under the
32
33 183 curve of mean blood pressure was estimated for each individual, over the first 24
34
35 184 hours, using polynomial integration and compared using the Wilcoxon rank sum test.
36
37 185 The proportion of patients reversing signs of hypoperfusion (mean blood pressure
38
39 186 (MAP) \geq 65 mm Hg, urine output \geq 0.5 mL/kg/h, CVP between 8 and 12 mmHg and
40
41 187 SvO₂ \geq 65%, within the first 6 hours of resuscitation) in the sepsis subgroup was
42
43 188 compared using the exact Fisher test.²⁶ We undertook complete cases analysis.
44
45 189 Since the current analysis was deemed exploratory and since we report on all
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47 190 statistical analysis done, no correction for multiples testing was deemed necessary.
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49 191 Statistical analyses were performed using SAS 9.3 (SAS Inc, Cary, NC) and R 2.13.0
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192 (<http://www.R-project.org/>) software. Tests were two sided. $P < 0.05$ was considered
193 significant.
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195 **Results**

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197 **Patients**

198 Among the CRISTAL population, 220 subjects had a PAC in place as part of their
199 routine management, of which 103 received colloids and 117 crystalloids, accounting
200 for a total of 645 catheter-days. PAC was placed mainly within 24 hours of
201 randomization ($n = 163$; 74%), either before ($n = 79$) or within 24 hours of
202 randomization ($n = 84$). Characteristics of the subgroup of PAC-monitored patients
203 were similar to those of the whole population of the CRISTAL study, regarding age,
204 gender and initial severity scores (Table 1). Median cumulative volume of fluid
205 administered during the first 7 days in the ICU was higher in the crystalloids than in
206 the colloids arm (3500 [2000 ;6000] vs. 2500 [1000 ;4000] ml respectively ($P = .01$)).
207 Supplemental table 2 displays the distribution of fluid types within each study arm.

208

209 **Treatments effects on hemodynamic variables**

210 Hemodynamic variables at the time of randomisation are described in Table 2.
211 Patients receiving colloids exhibited lower heart rate compared to those receiving
212 crystalloids ($P = .014$) (Figure 1). Systolic, diastolic and mean blood pressure did not
213 differ significantly between arms ($P = .6$, $P = .2$ and $P = .4$, respectively)
214 (supplemental Figures 1, 2 and 3). Cardiac index, although the difference was not
215 statistically significant ($P = .053$), was higher in colloids treated patients compared to
216 those treated with crystalloids (Figure 2). Central venous pressure did not differ
217 between both arms ($P = .9$) (supplemental Figure 4). Subjects in the colloids arm
218 exhibited a lower rate-pressure product, ($P = .036$) (Figure 3). Arterial pH, arterial
219 levels of bicarbonate and lactate did not differ between groups (respectively $P = .3$, P

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3 220 = .3 and $P = .9$) (supplemental Figures 5, 6 and 7). Mixed venous oxygen saturation
4
5 221 did not differ between both arms ($P = .9$). Daily urine output did not differ over time (P
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7 222 = .15). The SOFA score did not differ over time ($P = .3$).

8
9 223 Isotonic saline solutions and hydroxyl starches were the most common types of
10
11 224 administered fluids, among, respectively crystalloids and colloids groups. We
12
13 225 therefore compared the overall time-course of hemodynamic parameters between
14
15 226 isotonic saline treated patients and those treated with hydroxyethyl starches.
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17 227 Treatment with hydroxyethyl starches was associated with a lower heart rate ($P =$
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19 228 .023), and a lower rate pressure product ($P = .042$) compared to isotonic saline.
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24 230 **Sepsis subgroup**

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26 231 Among PAC-monitored patients, 108 subjects had sepsis, and 52 and 56 were
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28 232 allocated respectively to colloids and crystalloids. We compared the number of
29
30 233 patients achieving mean blood pressure levels ≥ 65 mm Hg and urine output ≥ 0.5
31
32 234 mL/kg/h within the first 6 hours. ²⁴ A total of 35/51 (69 %) patients in the crystalloids
33
34 235 arm achieved MAP ≥ 65 mm Hg after 6 hours vs. 31/47 (66%) in the colloids arm (P
35
36 236 = .8); 25/38 (66%) patients in the crystalloids arm achieved urine output ≥ 0.5
37
38 237 mL/kg/h after 6 hours vs. 17/28 (61%) in the colloids arm ($P = .8$). Limited data
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40 238 precluded the analysis of CVP and SvO₂ values during the first six hours following
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42 239 randomisation.
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3 241 **Discussion**

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7 243 We found that colloids achieved broadly similar resuscitation goals to crystalloids
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9 244 using lower volumes of administered fluids. Additionally, colloids may exhibit a
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11 245 favourable impact on heart rate and rate-pressure product. Colloids did not affect any
12
13 246 other hemodynamic endpoints. We found, in patients with sepsis, no evidence for a
14
15 247 superiority of colloids over crystalloids in achieving hemodynamic targets of the 6-
16
17 248 hour bundle of the Surviving Sepsis Campaign.²⁴ Tachycardia may increase
18
19 249 myocardial work, with subsequent excessive myocardial energy expenditure,²⁷ and
20
21 250 worse outcomes in the critically ill.^{28 29}

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23 251 The efficacy of fluid resuscitation is determined by the capacity of administered fluids
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25 252 to remain in the intravascular space.¹ The superior oncotic pressure of colloids is
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27 253 associated with increased intravascular expansion capacity compared to crystalloids.
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29 254 In order to achieve similar resuscitation goals, compared to colloids, between 20 and
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31 255 50% more volume of crystalloids should be administered.^{12 13 17 30} Inflammatory
32
33 256 states such as those observed during critical illness are usually associated with
34
35 257 endothelial dysfunction, leading to interstitial oedema. Reducing volumes of
36
37 258 administered fluids may be of clinical benefit and a negative fluid balance improved
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39 259 outcome in ARDS, a frequent complication of sepsis.^{31 32} By contrast, in septic
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41 260 shock, a positive fluid balance has been associated with a worse outcome.³³
42
43 261 However, colloid administration may be unsafe. Starches, the most commonly used
44
45 262 colloid, may be associated with increased risk of acute kidney injury and increased
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47 263 need for renal replacement therapy, both in the general ICU population and in sepsis.
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49 264^{12 13 16} The use of starches has now been restricted in the ICU in Europe and the US.

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3 266 Our findings are similar to those of several of the other major trials. Most trials
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5 267 compared one type of colloid to one type of crystalloid. The SAFE study compared
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7 268 4% albumin to 9‰ saline in critically ill patients.¹⁴ Albumin administration was
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9 269 associated with a statistically significant lower heart rate on the first day of treatment,
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11 270 although the difference was small. The ALBIOS study compared 20% albumin
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13 271 (titrated to achieve a serum albumin concentration of over 30 g/L) to 9‰ saline in
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15 272 patients suffering from severe sepsis.¹⁵ Over the first 7 days after randomization,
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17 273 patients in the albumin arm had lower heart rate and shorter duration of vasopressor
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19 274 therapy. The CHEST trial, compared hydroxyethyl starches to 9‰ saline for fluid
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21 275 resuscitation in critically ill patients.¹³ Among the various hemodynamic targets,
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23 276 higher central venous pressure over the first four days following randomization was
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25 277 the only statistically significant difference between hydroxyethyl starches and 9‰
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27 278 saline treated patients. The authors of the CHEST study concluded that crystalloids
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29 279 were as effective as colloids for initial resuscitation. The Scandinavian 6S trial
30
31 280 randomized patients with severe sepsis to receive either hydroxyethyl starches or
32
33 281 Ringer's acetate.¹² The hemodynamic targets were similar between both arms over
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35 282 the first 24 hours after randomization. Of note, subjects enrolled in both CHEST and
36
37 283 6S studies were enrolled up to 24 hours after their admission to the ICU, hence after
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39 284 the initial resuscitation phase.
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41 285 Our study has several limitations. First, our subgroup accounts for less than ten
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43 286 percent of the global CRISTAL trial population; the small size of our subgroup is
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45 287 related to a steady decline in the use of the pulmonary artery catheter during the
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47 288 CRISTAL trial, amidst reports that the use of pulmonary artery catheter does not alter
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49 289 outcome in ICU patients, and increased availability of less invasive hemodynamic
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51 290 monitoring tools. Moreover, some selection bias may have been introduced, due to
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3 291 the fact that PA catheterization was not performed within the 24 hours of
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5 292 randomization in about one fourth of the sample. Complete case analyses performed
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7 293 on available measurements further assumes that missing mechanisms were
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9 294 unrelated to patient status. Finally, some inflation of type I error rate associated with
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11 295 the number of tests undertaken is possible, meaning that interpretation of results
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13 296 should be exploratory.
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17
18 298 **Conclusion:** CRISTAL trial research participants with severe acute hypovolemic
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20 299 shock and monitored by a pulmonary artery catheter had lower heart rate when
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22 300 treated with colloids compared to crystalloids. As compared to colloids, crystalloids
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24 301 were as effective, though requiring higher volume, in reaching all other hemodynamic
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26 302 endpoints.
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3 305 **Authors' Contributions:** NH, SC, DA were involved in study concept and design;
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5 306 NH, SE, SJ, A-SD, JC, XF, AK, J-LT, JF, NA, MD, CM acquired the data; SC was
6
7 307 involved in the statistical analysis; NH, SC, DA were involved in analysis and
8
9 308 interpretation of data; NH and DA drafted the manuscript; all authors critically revised
10
11 309 the manuscript for important intellectual content; DA was involved in study
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13 310 supervision. All authors read and approved the final manuscript.
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17
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19
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21
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24
25 315 **Competing interests:** None declared.
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29 317 **Data sharing statement:** Individual data are available by contacting DA at
30
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34 319

35
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37
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40 322 Hospital for her technical assistance.
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324 Table 1. Main characteristics at baseline according to randomisation arm

	All patients n = 220	Colloids arm n = 103	Crystalloids arm n = 117
Age, median [IQR], y	68 [57 ;77]	69 [59 ;79]	67 [52 ;75]
Male sex, No. (%)	141 (64.1)	71 (68.9)	70 (59.8)
Weight, median [IQR], kg	72 [63 ;85]	71.3 [62.3 ;84.5]	73.4 [64 ;88]
Reason for ICU admission, No. (%)			
Medical	148 (67.3)	70 (68)	78 (66.7)
Scheduled surgery	41 (18.6)	20 (19.4)	21 (17.9)
Emergency surgery	29 (13.2)	12 (11.7)	17 (14.5)
Non-surgical trauma	2 (0.9)	1 (1)	1 (0.9)
Source of admission to ICU, No. (%)			
Community	104 (47.3)	39 (37.9)	65 (55.6)
Hospital ward	102 (46.4)	56 (54.4)	46 (39.3)
Other ICU	11 (5)	7 (6.8)	4 (3.4)
Long-term care facility	3 (1.3)	1 (0.9)	2 (1.7)
McCabe class, No. (%)			
No underlying disease or no fatal disease	129 (58.6)	62 (60.2)	67 (57.3)
Underlying ultimately fatal disease (>5y)	83 (37.7)	38 (36.9)	45 (38.5)
Underlying rapidly fatal disease (<1y)	8 (3.6)	3 (2.9)	5 (4.3)
Knaus disability scale, No. (%)			
A	35 (15.9)	15 (14.6)	20 (17.1)
B	82 (37.3)	33 (32)	49 (41.9)
C	64 (29.1)	33 (32)	31 (26.5)
D	37 (16.8)	20 (19.4)	17 (14.5)
Glasgow Coma Scale score, median [IQR]	11 [3 ;15]	13 [3 ;15]	11 [3 ;15]
SAPS II, median [IQR]	50 [33 ;65]	51 [36 ;66]	50 [30 ;64]
SOFA, median [IQR]	8 [5 ;11]	8 [5 ;11]	9 [5 ;12]
Sepsis, No. (%)	108 (49.1)	52 (50.5)	56 (47.9)

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327 ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score II; SOFA,
328 Sequential Organ Failure Assessment.

329 Knaus scale A: Prior good health, no functional limitations; B: Mild to moderate
330 limitation of activity because of chronic medical problem; C: Chronic disease
331 producing serious but not incapacitating restriction of activity; D: Severe restriction of
332 activity due to disease; includes persons bedridden or institutionalized due to illness.

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334 Table 2. Physiological values at baseline according to randomisation

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	All patients n = 220	Colloids arm n = 103	Crystalloids arm n = 117
Heart rate, median [IQR], beats/min (n = 218)	100 [89 ;120]	99 [88 ;115]	103.5 [90 ;124]
Systolic blood pressure, median [IQR], mm Hg (n = 219)	92 [76 ;109]	92.5 [73 ;108]	91 [80 ;111]
Diastolic blood pressure, median [IQR], mm Hg (n = 181)	48 [40 ;58]	47 [37 ;57]	50 [41 ;58]
Mean blood pressure, median [IQR], mm Hg (n = 184)	66 [56 ;77]	64.5 [53 ;75]	67 [60 ;78]
Central venous pressure, median [IQR], mm Hg (n = 81)	9 [7 ;12]	10 [6 ;12]	9 [7 ;13]
Pulmonary artery systolic pressure, median [IQR], mm Hg (n = 64)	32 [27 ;39]	32 [25 ;40]	32 [27 ;38]
Pulmonary artery diastolic pressure, median [IQR], mm Hg (n = 64)	17 [14 ;22]	16 [12 ;21]	18 [15 ;22]
Pulmonary artery mean pressure, median [IQR], mm Hg (n = 78)	22 [17 ;28]	21 [17 ;28]	23 [19 ;28]
Pulmonary artery occlusion pressure, median [IQR], mm Hg (n = 53)	12 [8 ;15]	12 [7 ;15]	12 [9 ;16]
Cardiac index, median [IQR], l/min/m ² (n = 75)	2.5 [2 ;3.1]	2.4 [2.2 ;3]	2.5 [2 ;3.3]
Systemic vascular resistance, median [IQR], dyn.s/cm ⁵ (n = 49)	893 [690 ;1208]	906 [699 ;1146]	830 [637 ;1238]
Pulmonary vascular resistance, median [IQR], dyn.s/cm ⁵ (n = 33)	170 [121 ;260]	170 [135 ;343]	172 [120 ;230]
Stroke volume index, median [IQR], ml/m ² (n = 74)	26 [21 ;34]	27 [22 ;34]	24 [20 ;33]
Left-ventricular stroke work index, median [IQR], g.m/m ² (n = 38)	20 [14 ;31]	20 [14 ;33]	17 [14 ;29]
Right ventricular stroke work index, median [IQR], g.m/m ² (n = 52)	5 [2 ;6]	4 [2 ;5]	5 [3 ;8]
pH, median [IQR] (n = 196)	7.34 [7.26 ;7.41]	7.36 [7.28 ;7.43]	7.33 [7.22 ;7.40]
HCO ₃ ⁻ , median [IQR], mmol/l (n = 110)	20.8 [17.6 ;24.2]	21.3 [17 ;24.6]	20 [18 ;23.6]
Lactate, median [IQR], mmol/l (n = 155)	2.3 [1.3 ;4.9]	2.3 [1.3 ;4.6]	2.25 [1.4 ;5]
SvO ₂ , median [IQR], % (n = 33)	71 [58 ;80]	63 [58 ;73]	74 [57 ;81]

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337 SvO₂: mixed venous oxygen saturation

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3 340 **Figure Legend**

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6 343 Figure 1: Box-plot showing heart rate distribution over the first seven days following
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8 344 randomisation in both arms.

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10 345 The horizontal line in the box indicates the median value while the lines at the top
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12 346 and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.

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19 349 following randomisation in both arms.

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23 351 and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.

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28 353 Figure 3: Box-plot showing the rate-pressure product distribution over the first seven
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30 354 days following randomisation in both arms.

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32 355 The horizontal line in the box indicates the median value while the lines at the top
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34 356 and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.

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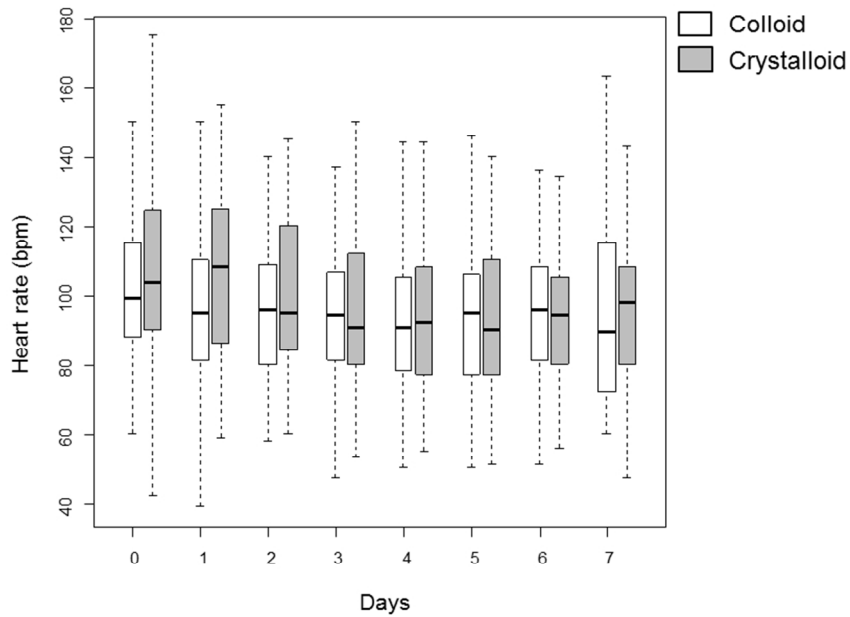


Figure 1

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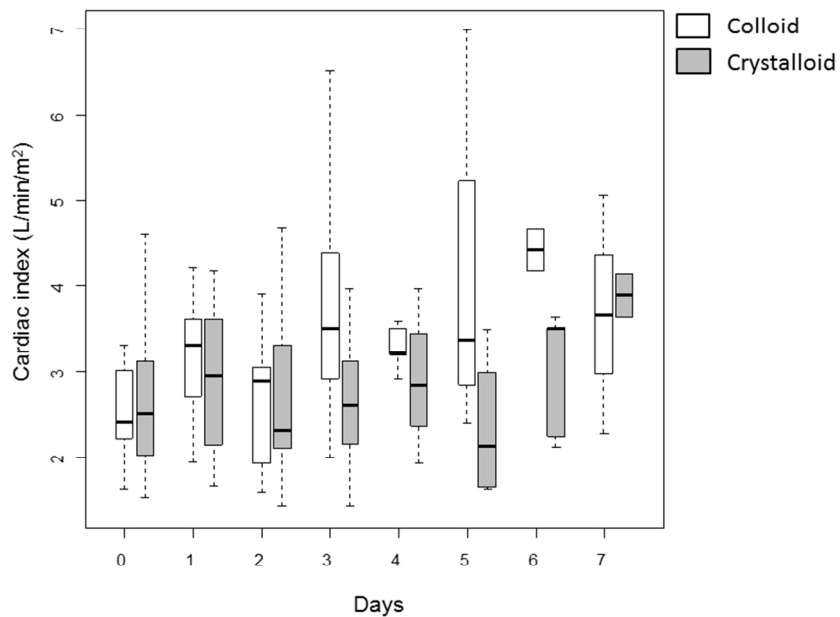


Figure 2

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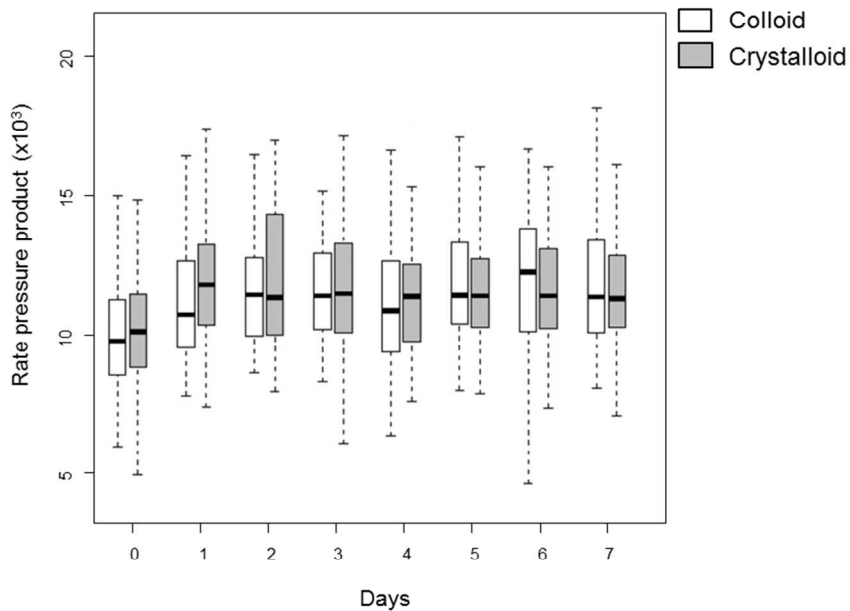


Figure 3

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SUPPLEMENTAL DATA

Hemodynamic Response to Crystalloids or Colloids in Shock: An Exploratory Subgroup Analysis of the CRISTAL Trial.

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⁴ Antoine Béclère Hospital, Clamart, France

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¹³ Biostatistic team, Saint Louis Hospital, Paris, France

Supplemental Table 1: Symptoms of acute hypovolemia at the time of inclusion

Variable	n = 220	Values Median (IQR) or %
Dizziness-n/total n (%)	43/90	47.8
Headache-n/total n (%)	10/82	12.2
Delirium-n/total n (%)	32/107	29.9
Thirst-n/total n (%)	19/78	24.4
Capillary refill time-seconds	29	3 [1 ;4]
Serum sodium-mmol/L	218	138 [135 ;141]
Protides-g/L	207	50 [40 ;59]
Albumin-g/L	114	22 [18 ;26.8]
Haematocrit-%	211	32 [28 ;37.5]
Blood urea nitrogen-mmol/L	219	0.56 [0.35 ;0.97]
Urinary output-ml/hour	207	46 [21.5 ;83]
Urinary sodium-mmol/L	99	42 [17 ;77]
Urinary urea nitrogen-mmol/L	91	8.4 [4.4 ;13.4]

Supplemental Table 2: Type of fluid administered by treatment group

	Colloids n= 103	Crystalloids n= 117
Isotonic saline-n(%)	14 (13.6)	107 (91.4)
Ringer's lactate-n(%)	2 (1.9)	21 (17.9)
Gelatins -n(%)	37 (35.9)	2 (1.7)
Hydroxyethyl Starch-n(%)	81 (78.7)	8 (6.8)
Albumin-n(%)	20 (19.4)	22 (18.8)

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3 Supplemental Figures
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7 Supplemental Figure 1: Box-plot showing systolic blood pressure distribution over the
8 first seven days following randomisation in both arms.
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11 The horizontal line in the box indicates the median value while the lines at the top
12 and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.
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17 Supplemental Figure 2: Box-plot showing diastolic blood pressure distribution over
18 the first seven days following randomisation in both arms.
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21 The horizontal line in the box indicates the median value while the lines at the top
22 and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.
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29 Supplemental Figure 3: Box-plot showing mean blood pressure distribution over the
30 first seven days following randomisation in both arms.
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33 The horizontal line in the box indicates the median value while the lines at the top
34 and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.
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40 Supplemental Figure 4: Box-plot showing central venous pressure distribution over
41 the first seven days following randomisation in both arms.
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44 The horizontal line in the box indicates the median value while the lines at the top
45 and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.
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51 Supplemental Figure 5: Box-plot showing pH distribution over the first seven days
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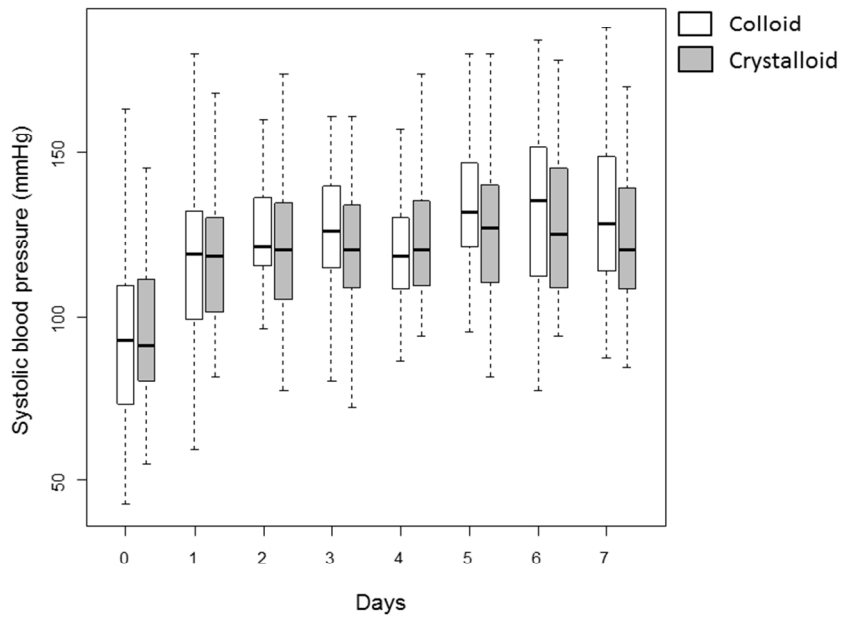
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10 Supplemental Figure 6: Box-plot showing blood bicarbonate distribution over the first
11 seven days following randomisation in both arms.
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15 and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.
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20 Supplemental Figure 7: Box-plot showing arterial lactate distribution over the first
21 seven days following randomisation in both arms.
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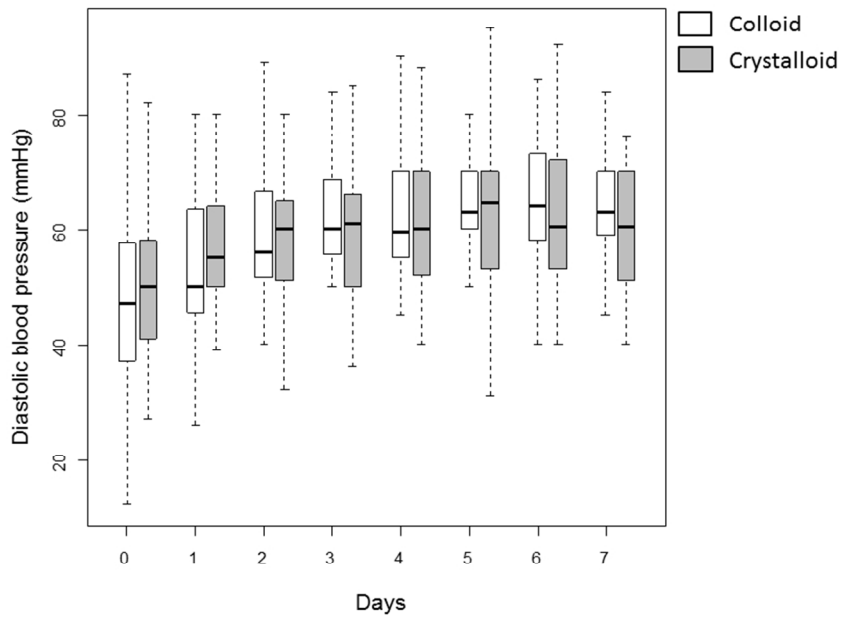


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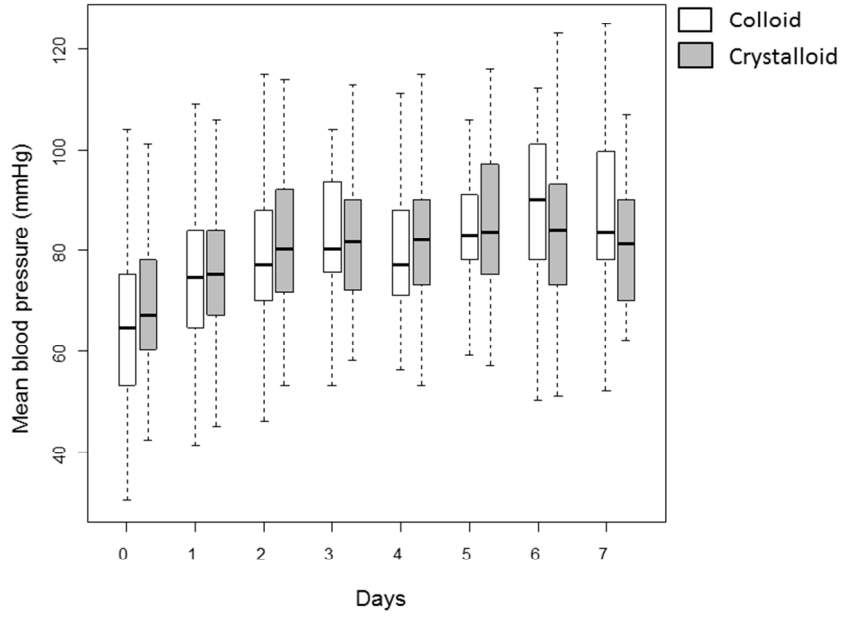
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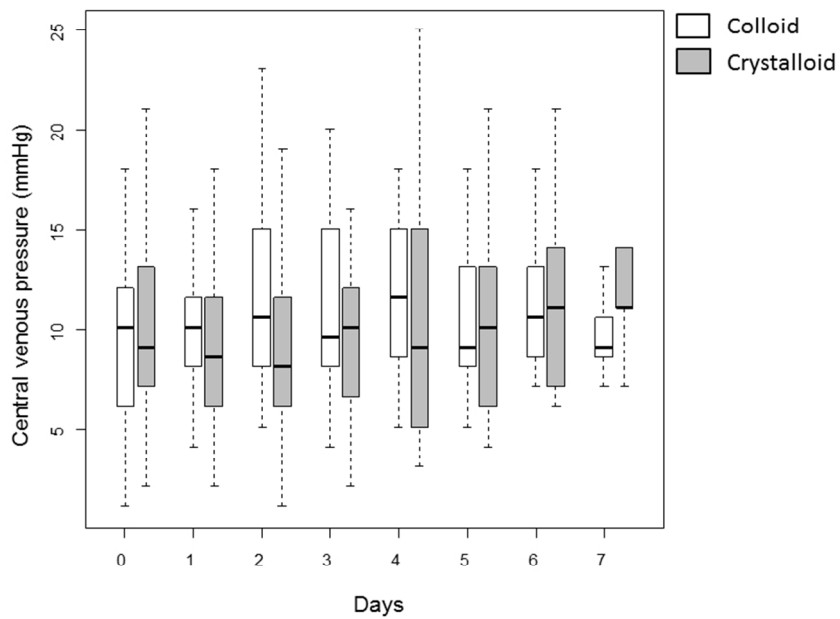


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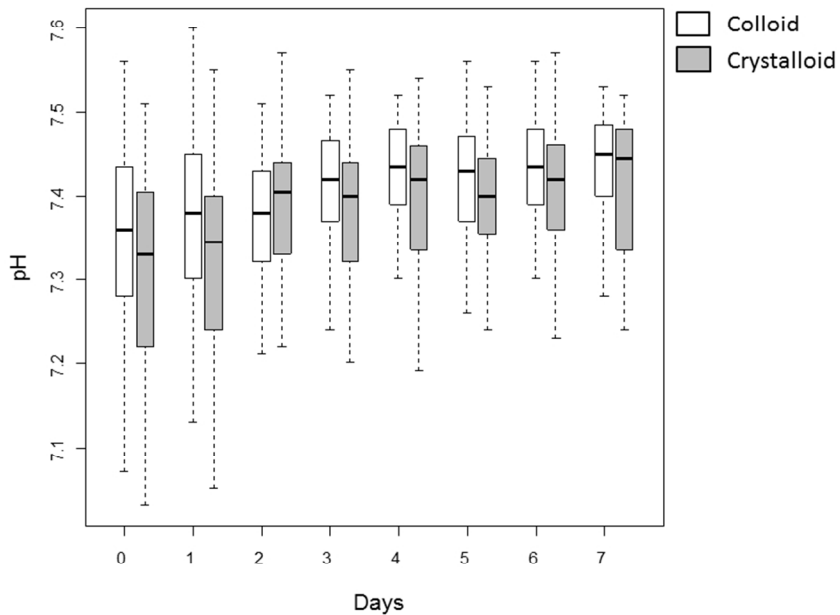
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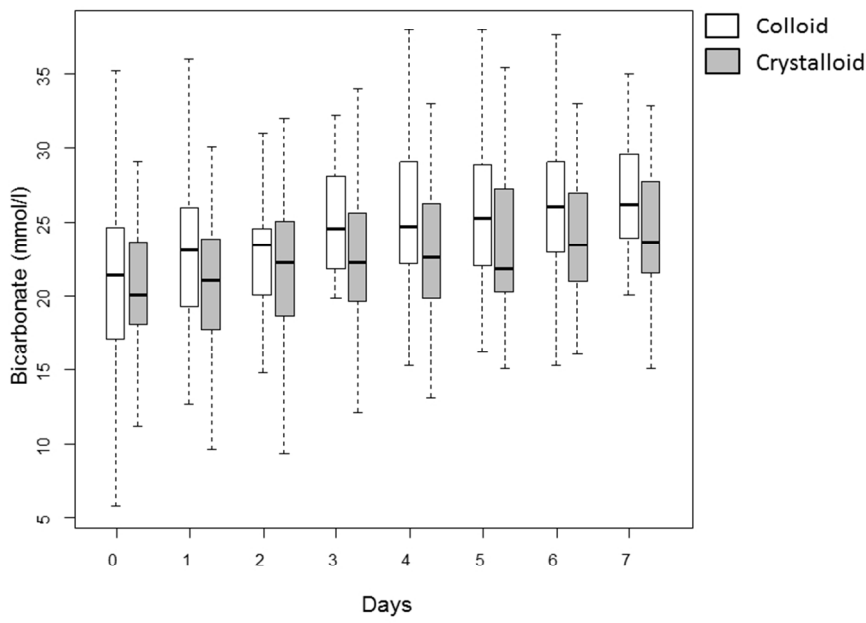
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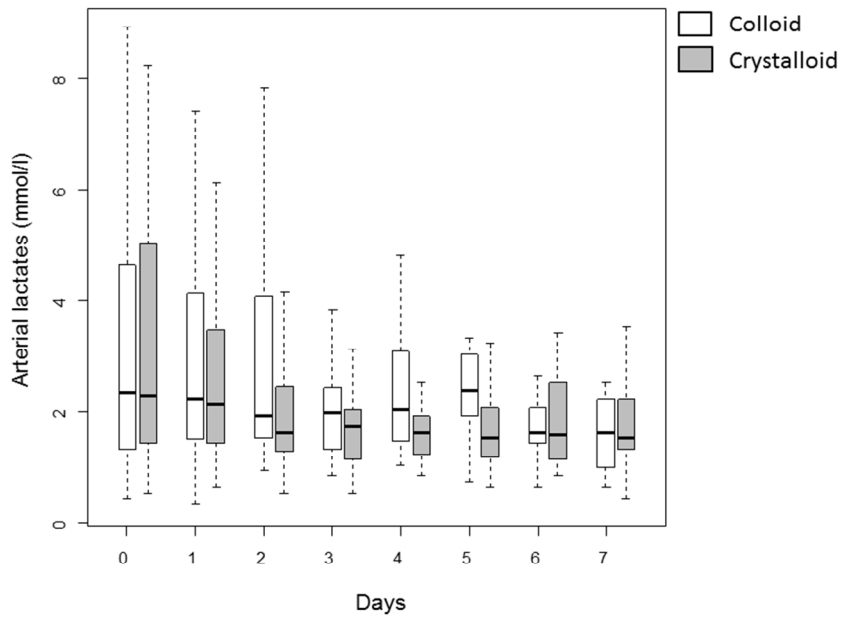
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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	na
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	na
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	6

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	na
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10
	13b	For each group, losses and exclusions after randomisation, together with reasons	na
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6
	14b	Why the trial ended or was stopped	6
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	16
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8-10-11
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10-11
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	na
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10-11
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	10-11
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	8-13-14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12-13-14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12-13-14
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	1
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Hemodynamic Response to Crystalloids or Colloids in Shock: An Exploratory Subgroup Analysis of a Randomized Controlled Trial.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-016736.R1
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Complete List of Authors:	heming, nicholas; Hopital Raymond-Poincare, General intensive care unit elatrous, souheil Jaber, S.; Montpellier Univ Hosp, Anesthesia and Critical Care dumenil, anne-sylvie cousson, Joël forceville, xavier kimmoun, antoine trouillet, jean-louis fichet, Jérôme anguel, nadia Darmon, M; Saint-Louis University Hospital martin, claud Chevret, Sylvie; Univ Paris Diderot Annane, D; Hopital Raymond-Poincare, General intensive care unit
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Fluid resuscitation, Intensive Care Unit (ICU), Pulmonary artery catheter, Crystalloid, Colloid

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Manuscripts

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3 1 **Hemodynamic Response to Crystalloids or Colloids in Shock: An Exploratory**
4 2 **Subgroup Analysis of a Randomized Controlled Trial.**

5 3
6 4 Heming, Nicholas MD¹; Elatrous, Souheil MD²; Jaber, Samir MD, PhD³; Dumenil,
7 5 Anne Sylvie MD⁴; Cousson, Joël MD⁵; Forceville, Xavier MD⁶; Kimmoun, Antoine
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36 Keywords: Fluid resuscitation; Crystalloid; Colloid; Pulmonary artery catheter;

37 Intensive Care Unit (ICU).

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1
2
3 47 **Abstract**
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11 Objective: To compare the hemodynamic effect of crystalloids and colloids during
12 acute severe hypovolemic shock.
13

14 Design: Exploratory subgroup analysis of a multicenter randomized controlled trial
15 (Colloids Versus Crystalloids for the Resuscitation of the Critically Ill, CRISTAL,
16 ClinicalTrials.gov NCT00318942).
17

18 Setting: CRISTAL was conducted in ICUs in Europe, North Africa, and Canada.
19

20 Participants: Current analysis included all patients who had a pulmonary artery
21 catheter in place at randomisation. 220 patients (117 received crystalloids vs. 103
22 colloids) underwent pulmonary artery catheterization.
23
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26 Intervention: Crystalloids versus colloids for fluid resuscitation in hypovolemic shock.
27

28 Outcome measures: Hemodynamic data were collected at the time of randomization
29 and subsequently on days 1, 2, 3, 4, 5, 6, 7.
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32 Results: Median cumulative volume of fluid administered during the first 7 days was
33 higher in the crystalloids group than in the colloids group (3500 [2000 ;6000] vs. 2500
34 [1000 ;4000] ml, $P = .01$). Patients in the colloids arm exhibited a lower heart rate
35 over time compared to those allocated to the crystalloids arm ($P = .014$). There was
36 no significant difference in cardiac index ($P = .053$), mean blood pressure ($P = .4$),
37 arterial lactates ($P = .9$) or global SOFA score ($P = .3$) over time between arms.
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47 Conclusions: During acute severe hypovolemic shock, patients monitored by a
48 pulmonary artery catheter achieved broadly similar hemodynamic outcomes, using
49 lower volumes of colloids than crystalloids. The heart rate was lower in the colloids
50 arm.
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3 72 Strengths of the study include:

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5 73 • Large international multicenter trial, comparing the hemodynamic effect of
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7 74 crystalloids vs. colloids in severe hypovolemic shock. The subgroup analysis
8
9 75 met recognized criteria of robustness.
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12 76 • The CRISTAL trial was a pragmatic, open label trial.

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16 77 Limitations of the study include:

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18 78 • Pulmonary artery catheter monitoring was left at the patient's physician
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20 79 discretion resulting in missing data.
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23 80 • Results should be considered exploratory.
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82 Introduction

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84 Fluid resuscitation is a cornerstone of the management of hypovolemia.¹ During
85 hypovolemic shock, fluids restore intravascular volume, cardiac output, oxygen
86 delivery and reverse peripheral hypoperfusion.² Resuscitation fluids are divided into
87 two distinct categories, crystalloids and colloids.³ On the one hand, crystalloids dilute
88 the plasma protein content, reducing plasma oncotic pressure which may result in
89 interstitial oedema. The most commonly used crystalloid, isotonic saline, induces
90 hyperchloremic acidosis and acute kidney injury.^{4 5 6} On the other hand, colloids are
91 composed of large molecules, increasing their vascular retention and are theoretically
92 more effective for fluid resuscitation.^{7 8} However, the most commonly used colloid,
93 starch, is associated with acute kidney injury, increased need for renal replacement
94 therapy, accumulation in reticuloendothelial tissues, and increased requirements for
95 blood products.⁹⁻¹¹ A series of large clinical trials were recently undertaken aiming at
96 determining which fluid was superior for the resuscitation of critically ill patients.¹²⁻¹⁶

97 The Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL)
98 trial addressed the issue using a pragmatic approach; rather than studying one fluid
99 versus another, both categories of fluids, crystalloids and colloids were compared in
100 severe hypovolemia.¹⁷ The CRISTAL trial included 2857 subjects treated in 57
101 intensive care units (ICU). The primary outcome, 28 day mortality, did not
102 significantly differ, with 25.4% mortality in the colloids arm vs. 27% in the crystalloids
103 arm. This finding was similar to results from previous large trials comparing a single
104 colloid to a single crystalloid.¹³⁻¹⁵ However, mortality by 90 days was significantly
105 lower in the colloids arm than in the crystalloids arm (30.7% vs. 34.2%). This finding
106 was deemed exploratory. Additionally, the number of days alive at 7 and 28 days

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3 107 without vasopressor therapy was higher in the colloids than in the crystalloids arm.
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5 108 We sought to compare the effect of crystalloids to that of colloids on hemodynamic
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7 109 parameters during hypovolemic shock. The pulmonary artery catheter (PAC)
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9 110 provides a reliable and reproducible measure of cardiac output as well as the
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11 111 pulmonary artery pressure, pulmonary artery occlusion pressure and derived
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13 112 variables.¹⁸ Therefore, the current study aimed at assessing the hemodynamic effect
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15 113 of crystalloids vs. colloids in the CRISTAL participants monitored by pulmonary artery
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17 114 catheter.
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116 **Materials and Methods**

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118 1) Study setting and patients

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120 The current study is a subgroup analysis of a randomized multicentre trial (CRISTAL,
121 ClinicalTrials.gov NCT00318942), comparing the effect of crystalloid vs. colloid
122 administration for fluid resuscitation in the intensive care unit on mortality at 28 days.

123 ¹⁷ CRISTAL was a non-blinded, pragmatic study. Included subjects were randomized
124 to receive either crystalloids or colloids for hypovolemia. Crystalloids consisted of
125 isotonic or hypertonic saline as well as buffered solutions, while colloids comprised
126 albumin, gelatins, dextrans and hydroxyethyl starches. Patients were managed
127 throughout their ICU stay with the same fluid category. The type of fluid within the
128 assigned group as well as the amount of fluid to be administered was determined by
129 the physician in charge of the patient, the daily total dose of hydroxyethyl starch
130 being restricted to no more than 30 mL/kg of body weight. Physicians could
131 administer albumin in response to demonstrated hypoalbuminemia. ¹⁷ The study
132 protocol was approved by local institutional review boards. Deferred informed
133 consent was obtained from participants or legally authorized surrogates.

134 For the current ancillary study, among the CRISTAL population, we included all
135 patients who had a PAC in place as part of their routine management either prior to
136 or within the first 24 hours of randomization.

137

138 2) Data collection

139 Demographic and general characteristics

140 The following data were prospectively collected at the time of randomization: age,
141 gender, weight, source of admission, McCabe class ¹⁹ and disability scale score. ²⁰

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3 142 Severity scores including the Glasgow coma score,²¹ Simplified Acute Physiology
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5 143 Score II (SAPS II)²² and the Sequential Organ Failure Assessment (SOFA) Score.²³
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7 144 Causes of acute hypovolemia were stratified in the initial trial as sepsis, trauma or
8
9 145 other disorders. We collected a set of symptoms and biological signs of acute
10
11 146 hypovolemia (Table S1).

147 Hemodynamic variables

148 We prospectively measured, for as long as the PAC was in place or up to seven days
149 (whichever occurred first), before randomisation and then once daily (by recording
150 the first value reported in the medical file following the change of shift, i.e. typically
151 around 08h00) the following hemodynamic data: heart rate, systolic, diastolic and
152 mean blood pressure, central venous pressure (CVP), systolic, diastolic and mean
153 pulmonary artery pressure, pulmonary artery occlusion pressure (PAOP), cardiac
154 index, and urinary output. Additionally, mean blood pressure was recorded hourly
155 following the first 24 hours after randomisation. We calculated, using standard
156 formulas, the product of the heart rate and systolic blood pressure (or rate-pressure
157 product, RPP), a marker of myocardial perfusion requirement, systemic and
158 pulmonary vascular resistances, stroke volume index, left and right ventricular stroke
159 work index. Laboratory values included arterial pH, bicarbonate, lactate and SvO₂.
160 Finally, to compare colloids to crystalloids in reaching the hemodynamic targets of
161 the 6-hour bundles of the Surviving Sepsis campaign, we collected these same
162 variables, six hours after randomisation.²⁴

163

164 Other variables

165 We collected before randomisation and daily up to seven days post randomization,
166 the SOFA score and the cumulative volume of administered fluids and throughout the

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3 167 trial the occurrence of the main interventions including, packed red blood cell
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5 168 transfusion and the administration of vasopressors.
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10 170 3) Statistical analysis

11 171 Quantitative variables are expressed as median [interquartile range] and categorical
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13 172 variables as number (percentage). The 7 day time course of mean, systolic and
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15 173 diastolic blood pressure, central venous pressure, heart rate, cardiac index, and daily
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17 174 diuresis as well as the results of arterial blood gases were compared between arms.
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19 175 We then compared systolic, diastolic and mean pulmonary artery pressure and
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21 176 pulmonary artery occlusion pressure in both arms. In order to further explore
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23 177 differences between arms, we calculated the rate pressure product as well as the
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25 178 various indexes derived from the use of the PAC. Mixed effects models, which are
26
27 179 appropriate for clustered and dependent data, were used to study the relationship
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29 180 between treatment arms and the time course of hemodynamic variables as well as
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31 181 the global SOFA score.²⁵ The area under the curve of mean blood pressure was
32
33 182 estimated for each individual, over the first 24 hours, using polynomial integration and
34
35 183 compared using the Wilcoxon rank sum test. Number of days alive without
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37 184 vasopressor therapy was compared using the Wilcoxon rank sum test. The
38
39 185 proportion of patients reversing signs of hypoperfusion (mean blood pressure (MAP)
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41 186 ≥ 65 mm Hg, urine output ≥ 0.5 mL/kg/h, CVP between 8 and 12 mmHg and SvO₂ \geq
42
43 187 65%, within the first 6 hours of resuscitation) in the sepsis subgroup was compared
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45 188 using the exact Fisher test.²⁶ Complete cases analysis was undertaken. Since the
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47 189 current analysis was deemed exploratory and since we report on all statistical
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49 190 analysis done, no correction for multiples testing was deemed necessary. Statistical
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51 191 analyses were performed using SAS 9.3 (SAS Inc, Cary, NC) and R 2.13.0
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192 (<http://www.R-project.org/>) software. Tests were two sided. $P < 0.05$ was considered
193 significant.
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195 **Results**

196

197 **Patients**

198 Among the CRISTAL population, 220 subjects had a PAC in place as part of their
199 routine management, of which 103 received colloids and 117 crystalloids, accounting
200 for a total of 645 catheter-days. PAC was generally in place around the time of
201 randomization, either before ($n = 79$; 36%) or within 24 hours post randomization ($n =$
202 84; 38%). Characteristics of the subgroup of PAC-monitored patients were similar to
203 those of the whole population of the CRISTAL study, regarding age, gender and
204 initial severity scores (Table 1). Hemodynamic variables at the time of randomisation
205 are described in Table 2.

206

207 **Treatment effects on hemodynamic variables**

208 Median cumulative volume of fluid administered during the first 7 days in the ICU was
209 higher in the crystalloids than in the colloids arm (3500 [2000 ;6000] vs. 2500 [1000
210 ;4000] ml respectively ($P = .01$)). The distribution of fluid types within each study arm
211 is displayed in the supplementary files (Table S2). During the first 24 hours following
212 randomisation, mean blood pressure did not significantly differ between treatment
213 arm (mean area under the curve 78 [68 ;84] for colloids vs. 77 [70 ;84] mmHg/h for
214 crystalloids ($P = .6$)). The heart rate was lower in the colloids than in the crystalloids
215 group ($P = .014$) (Figure 1). Systolic, diastolic and mean blood pressure did not
216 significantly differ between arms ($P = .6$, $P = .2$ and $P = .4$, respectively) (Figures S1,
217 S2 and S3). Cardiac index, although the difference was not statistically significant (P
218 = .053), was higher in colloids treated patients compared to those treated with
219 crystalloids (Figure 2). Central venous pressure did not differ between both arms ($P =$

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3 220 .9) (Figure S4). Subjects in the colloids arm exhibited a lower rate-pressure product,
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5 221 ($P = .036$) (Figure 3). Arterial pH, arterial levels of bicarbonate and lactate did not
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7 222 differ between groups ($P = .3$, $P = .3$ and $P = .9$, respectively) (Figures S5, S6 and
8
9 223 S7). Mixed venous oxygen saturation, daily urine output (Figure S8), and the SOFA
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11 224 score did not differ between both arms ($P = .9$, $P = .15$ and $P = .3$, respectively).
12
13 225 Hemodynamic stability was reached through a similar use of vasopressors and a
14
15 226 similar use of blood transfusion (Table 3). Other relevant outcomes did not
16
17 227 significantly differ between both groups. No serious adverse event related to PAC
18
19 228 placement was reported during the trial.

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23 229 Isotonic saline solutions and hydroxyl starches were the most common types of
24
25 230 administered fluids, among, respectively crystalloids and colloids groups. We
26
27 231 therefore compared the overall time-course of hemodynamic parameters between
28
29 232 isotonic saline treated patients and those treated with hydroxyethyl starches.
30
31 233 Treatment with hydroxyethyl starches was associated with a lower heart rate ($P =$
32
33 234 $.023$), and a lower rate pressure product ($P = .042$) compared to isotonic saline.
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37 38 236 **Sepsis subgroup**

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40 237 Among PAC-monitored patients, 108 subjects were stratified in the sepsis group, of
41
42 238 which 52 were allocated to colloids and 56 to crystalloids. We compared the number
43
44 239 of patients achieving mean blood pressure levels ≥ 65 mm Hg and urine output ≥ 0.5
45
46 240 mL/kg/h within the first 6 hours. ²⁴ A total of 35/51 (69 %) patients in the crystalloids
47
48 241 arm achieved MAP ≥ 65 mm Hg after 6 hours vs. 31/47 (66%) in the colloids arm (P
49
50 242 = $.8$); 25/38 (66%) patients in the crystalloids arm achieved urine output ≥ 0.5
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52 243 mL/kg/h after 6 hours vs. 17/28 (61%) in the colloids arm ($P = .8$). Limited data
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3 244 precluded the analysis of CVP and SvO₂ values during the first six hours following
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5 245 randomisation.
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3 247 **Discussion**

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7 249 We found that colloids achieved broadly similar resuscitation goals to crystalloids
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9 250 using lower volumes of administered fluids. Additionally, colloids may exhibit a
10
11 251 favourable impact on heart rate and rate-pressure product. Colloids did not affect any
12
13 252 other hemodynamic endpoints. We found, in patients with sepsis, no evidence for a
14
15 253 superiority of colloids over crystalloids in achieving hemodynamic targets of the 6-
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17 254 hour bundle of the Surviving Sepsis Campaign.²⁴ The fact that the mean arterial
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19 255 blood pressure and cardiac index did not significantly differ in both groups may be
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21 256 explained by the fact that physicians sought to achieve similar targets in both groups,
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23 257 whether by the administration of fluids, packed blood or vasopressors.

24
25 258 Tachycardia may increase myocardial work, with subsequent excessive myocardial
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27 259 energy expenditure,²⁷ and may be associated with worse outcomes through
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29 260 excessive cardiovascular morbi-mortality.^{28 29} Myocardial protection is of particular
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31 261 interest in the aging population currently common in most ICUs, since it may
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33 262 somewhat relieve cardiovascular mortality.

34
35 263 The efficacy of fluid resuscitation is determined by the capacity of administered fluids
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37 264 to remain in the intravascular space.¹ The superior oncotic pressure of colloids is
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39 265 associated with increased intravascular expansion capacity compared to crystalloids.
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41 266 In order to achieve similar resuscitation goals, compared to colloids, between 20 and
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43 267 50% more volume of crystalloids should be administered.^{12 13 17 30} Inflammatory
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45 268 states such as those observed during critical illness are usually associated with
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47 269 endothelial dysfunction, leading to interstitial oedema. Reducing volumes of
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49 270 administered fluids may be of clinical benefit and a negative fluid balance improved
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51 271 outcome in ARDS, a frequent complication of sepsis.^{31 32} In septic shock, a positive
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3 272 fluid balance has been associated with a worse outcome.³³ However, short term
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5 273 hemodynamic benefits of fluids may in some cases be offset by long term deleterious
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7 274 consequences. Indeed, some types of colloids may be unsafe. Starches, the most
8
9 275 commonly used colloid, may be associated with increased risk of acute kidney injury
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11 276 and increased need for renal replacement therapy, both in the general ICU
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13 277 population and in sepsis.^{12 13 16} The daily total volume of hydroxyethyl starch which
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15 278 could not exceed 30ml/kg in the CRISTAL trial, lead patients having exceeded that
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17 279 limit to subsequently receive crystalloids. The use of starches has now been
18
19 280 restricted in the ICU in Europe and the US.^{34 35} The implication is that from a
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21 281 hemodynamic point of view, fluid resuscitation with colloids or crystalloids is broadly
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23 282 equivalent - maybe with a slight advantage for colloids - although the price of
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25 283 resuscitation using crystalloids would be an increase in the total volume of
26
27 284 administered fluids.

28 285 Our findings are similar to those of several of the other major fluid trials. Most trials
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30 286 compared one type of colloid to one type of crystalloid. The SAFE study assessed
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32 287 4% albumin or 9% saline in critically ill patients.¹⁴ Albumin administration was
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34 288 associated with a statistically significant lower heart rate on the first day of treatment,
35
36 289 although the difference was small. The ALBIOS study compared 20% albumin
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38 290 (titrated to achieve a serum albumin concentration of over 30 g/L) to 9% saline in
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40 291 patients suffering from severe sepsis.¹⁵ Over the first 7 days after randomization,
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42 292 patients in the albumin arm experienced lower heart rate and a shorter duration of
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44 293 vasopressor therapy. The CHEST trial randomized critically ill patients to receive
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46 294 hydroxyethyl starches or 9% saline.¹³ Among the various hemodynamic targets,
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48 295 higher central venous pressure over the first four days following randomization was
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50 296 the only statistically significant difference between hydroxyethyl starches and 9%

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3 297 saline treated patients. The authors of the CHEST study concluded that crystalloids
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5 298 were as effective as colloids for initial resuscitation. The Scandinavian 6S trial
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7 299 allocated either hydroxyethyl starches or Ringer's acetate to severe sepsis patients.
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9 300 ¹² The hemodynamic targets were similar between both arms over the first 24 hours
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11 301 after randomization. Of note, subjects enrolled in both CHEST and 6S studies were
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13 302 enrolled up to 24 hours after their admission to the ICU, hence after the initial
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15 303 resuscitation phase. However, in CRISTAL, patients were randomized and treated as
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17 304 early as possible after the occurrence of shock. Patients in CRISTAL were treated by
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19 305 a variety of colloids including starches, but also gelatins, in approximately a third of
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21 306 patients. Gelatins have been less extensively studied in large clinical trials and their
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23 307 drawbacks are not as well characterised. Their use may have somewhat offset any
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25 308 deleterious effect related to starches when administered in the colloid group. Overall
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27 309 these findings should help expand our knowledge pertaining to the field of fluid
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29 310 resuscitation.
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36 312 Our study has some limitations. First, our subgroup accounts for less than ten
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38 313 percent of the global CRISTAL trial population; the small size of our subgroup is
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40 314 related to a steady decline in the use of the pulmonary artery catheter during the
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42 315 CRISTAL trial, amidst reports that the use of pulmonary artery catheter does not alter
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44 316 outcome in ICU patients, and increased availability of less invasive hemodynamic
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46 317 monitoring tools. Moreover, some selection bias may have been introduced, due to
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48 318 the fact that PA catheterization was not performed within the 24 hours of
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50 319 randomization in about one fourth of the sample. Complete case analyses performed
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52 320 on available measurements further assumes that missing mechanisms were
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54 321 unrelated to patient status. Finally, some inflation of type I error rate associated with
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3 322 the number of tests undertaken is possible, meaning that interpretation of results
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5 323 should be exploratory.
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9 325 **Conclusion:** CRISTAL participants monitored by a pulmonary artery catheter
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11 326 reached broadly similar hemodynamic outcomes whether treated by crystalloids or by
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13 327 colloids. Colloids were associated with lower heart rates and lower volume of
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15 328 administered fluids than crystalloids.
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3 330 **Authors' Contributions:** NH, SC, DA were involved in study concept and design;
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5 331 NH, SE, SJ, A-SD, JC, XF, AK, J-LT, JF, NA, MD, CM acquired the data; SC was
6
7 332 involved in the statistical analysis; NH, SC, DA were involved in analysis and
8
9 333 interpretation of data; NH and DA drafted the manuscript; all authors critically revised
10
11 334 the manuscript for important intellectual content; DA was involved in study
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13 335 supervision. All authors read and approved the final manuscript.
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28 342 **Data sharing statement:** Individual data are available by contacting DA at
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30 343 djillali.annane@aphp.fr
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349 Table 1. Main characteristics at baseline according to randomisation arm

	All patients n = 220	Colloids arm n = 103	Crystalloids arm n = 117	P-value
Age, median [IQR], y	68 [57 ;77]	69 [59 ;79]	67 [52 ;75]	0.05
Male sex, No. (%)	141 (64.1)	71 (68.9)	70 (59.8)	0.20
Weight, median [IQR], kg	72 [63 ;85]	71.3 [62.3 ;84.5]	73.4 [64 ;88]	0.49
Reason for ICU admission, No. (%)				0.58
Medical	148 (67.3)	70 (68)	78 (66.7)	
Scheduled surgery	41 (18.6)	20 (19.4)	21 (17.9)	
Emergency surgery	29 (13.2)	12 (11.7)	17 (14.5)	
Non-surgical trauma	2 (0.9)	1 (1)	1 (0.9)	
Source of admission to ICU, No. (%)				0.11
Community	104 (47.3)	39 (37.9)	65 (55.6)	
Hospital ward	102 (46.4)	56 (54.4)	46 (39.3)	
Other ICU	11 (5)	7 (6.8)	4 (3.4)	
Long-term care facility	3 (1.3)	1 (0.9)	2 (1.7)	
McCabe class, No. (%)				0.83
No underlying disease or no fatal disease	129 (58.6)	62 (60.2)	67 (57.3)	
Underlying ultimately fatal disease (>5y)	83 (37.7)	38 (36.9)	45 (38.5)	
Underlying rapidly fatal disease (<1y)	8 (3.6)	3 (2.9)	5 (4.3)	
Knaus disability scale, No. (%)				0.28
A	35 (15.9)	15 (14.6)	20 (17.1)	
B	82 (37.3)	33 (32)	49 (41.9)	
C	64 (29.1)	33 (32)	31 (26.5)	
D	37 (16.8)	20 (19.4)	17 (14.5)	
Glasgow Coma Scale score, median [IQR]	11 [3 ;15]	13 [3 ;15]	11 [3 ;15]	0.61
SAPS II, median [IQR]	50 [33 ;65]	51 [36 ;66]	50 [30 ;64]	0.41
SOFA, median [IQR]	8 [5 ;11]	8 [5 ;11]	9 [5 ;12]	0.80
Sepsis, No. (%)	108 (49.1)	52 (50.5)	56 (47.9)	0.79

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352 ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score II; SOFA,
353 Sequential Organ Failure Assessment.

354 Knaus scale A: Prior good health, no functional limitations; B: Mild to moderate
355 limitation of activity because of chronic medical problem; C: Chronic disease
356 producing serious but not incapacitating restriction of activity; D: Severe restriction of
357 activity due to disease; includes persons bedridden or institutionalized due to illness.

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359 Table 2. Physiological values at baseline according to randomisation

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	All patients n = 220	Colloids arm n = 103	Crystalloids arm n = 117	P- value
Heart rate, median [IQR], beats/min (n = 218)	100 [89 ;120]	99 [88 ;115]	103.5 [90 ;124]	0.25
Systolic blood pressure, median [IQR], mm Hg (n = 219)	92 [76 ;109]	92.5 [73 ;108]	91 [80 ;111]	0.89
Diastolic blood pressure, median [IQR], mm Hg (n = 181)	48 [40 ;58]	47 [37 ;57]	50 [41 ;58]	0.19
Mean blood pressure, median [IQR], mm Hg (n = 184)	66 [56 ;77]	64.5 [53 ;75]	67 [60 ;78]	0.21
Central venous pressure, median [IQR], mm Hg (n = 81)	9 [7 ;12]	10 [6 ;12]	9 [7 ;13]	0.96
Pulmonary artery systolic pressure, median [IQR], mm Hg (n = 64)	32 [27 ;39]	32 [25 ;40]	32 [27 ;38]	0.59
Pulmonary artery diastolic pressure, median [IQR], mm Hg (n = 64)	17 [14 ;22]	16 [12 ;21]	18 [15 ;22]	0.24
Pulmonary artery mean pressure, median [IQR], mm Hg (n = 78)	22 [17 ;28]	21 [17 ;28]	23 [19 ;28]	0.51
Pulmonary artery occlusion pressure, median [IQR], mm Hg (n = 53)	12 [8 ;15]	12 [7 ;15]	12 [9 ;16]	0.30
Cardiac index, median [IQR], l/min/m ² (n = 75)	2.5 [2 ;3.1]	2.4 [2.2 ;3]	2.5 [2 ;3.3]	0.94
Systemic vascular resistance, median [IQR], dyn.s/cm ⁵ (n = 49)	893 [690 ;1208]	906 [699 ;1146]	830 [637 ;1238]	0.40
Pulmonary vascular resistance, median [IQR], dyn.s/cm ⁵ (n = 33)	170 [121 ;260]	170 [135 ;343]	172 [120 ;230]	0.35
Stroke volume index, median [IQR], ml/m ² (n = 74)	26 [21 ;34]	27 [22 ;34]	24 [20 ;33]	0.40
Left-ventricular stroke work index, median [IQR], g.m/m ² (n = 38)	20 [14 ;31]	20 [14 ;33]	17 [14 ;29]	0.73
Right ventricular stroke work index, median [IQR], g.m/m ² (n = 52)	5 [2 ;6]	4 [2 ;5]	5 [3 ;8]	0.12
pH, median [IQR] (n = 196)	7.34 [7.26 ;7.41]	7.36 [7.28 ;7.43]	7.33 [7.22 ;7.40]	0.038
HCO ₃ ⁻ , median [IQR], mmol/l (n = 110)	20.8 [17.6 ;24.2]	21.3 [17 ;24.6]	20 [18 ;23.6]	0.44
Lactate, median [IQR], mmol/l (n = 155)	2.3 [1.3 ;4.9]	2.3 [1.3 ;4.6]	2.25 [1.4 ;5]	0.94
SvO ₂ , median [IQR], % (n = 33)	71 [58 ;80]	63 [58 ;73]	74 [57 ;81]	0.31

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362 SvO₂: mixed venous oxygen saturation

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365 Table 3. Study outcome and blood transfusion by treatment group

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	Colloids arm (n = 103)	Crystalloids arm (n = 117)	P-value
No. of days alive without, median [IQR]			
Vasopressor therapy within the first 28 d	18 [0 ;25]	20 [0 ;24]	0.98
Units of packed red blood cell transfused, median [IQR]	2 [2 ; 3]	2 [2 ; 4]	0.59

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3 370 **Figure Legend**

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6 373 Figure 1: Box-plot showing heart rate distribution over the first seven days following
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8 374 randomisation in both arms.

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10 375 The horizontal line in the box indicates the median value while the lines at the top
11 376 and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.

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17 378 Figure 2: Box-plot showing cardiac index distribution over the first seven days
18 379 following randomisation in both arms.

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21 380 The horizontal line in the box indicates the median value while the lines at the top
22 381 and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.

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27 383 Figure 3: Box-plot showing the rate-pressure product distribution over the first seven
28 384 days following randomisation in both arms.

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31 385 The horizontal line in the box indicates the median value while the lines at the top
32 386 and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.

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23 477 should no longer be used in patients with sepsis or burn injuries or in critically ill patients.
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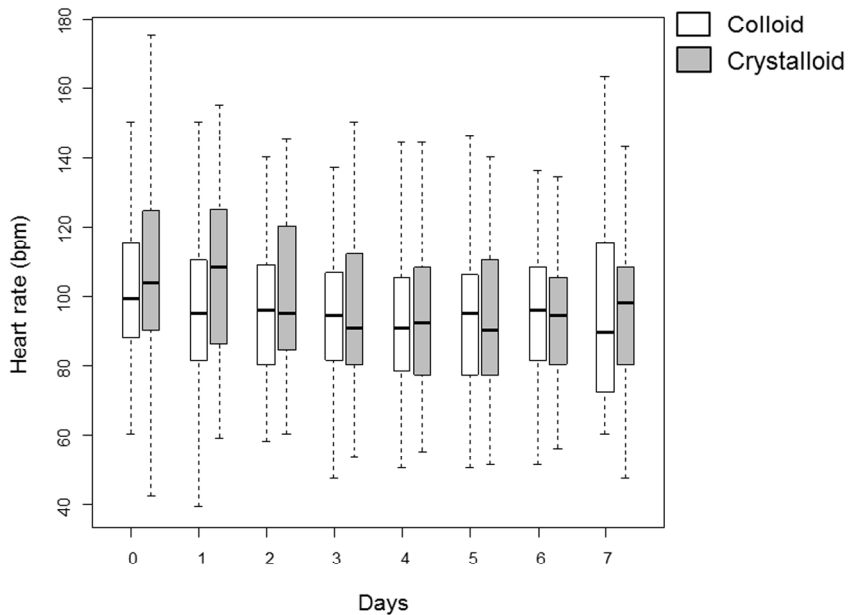


Figure1

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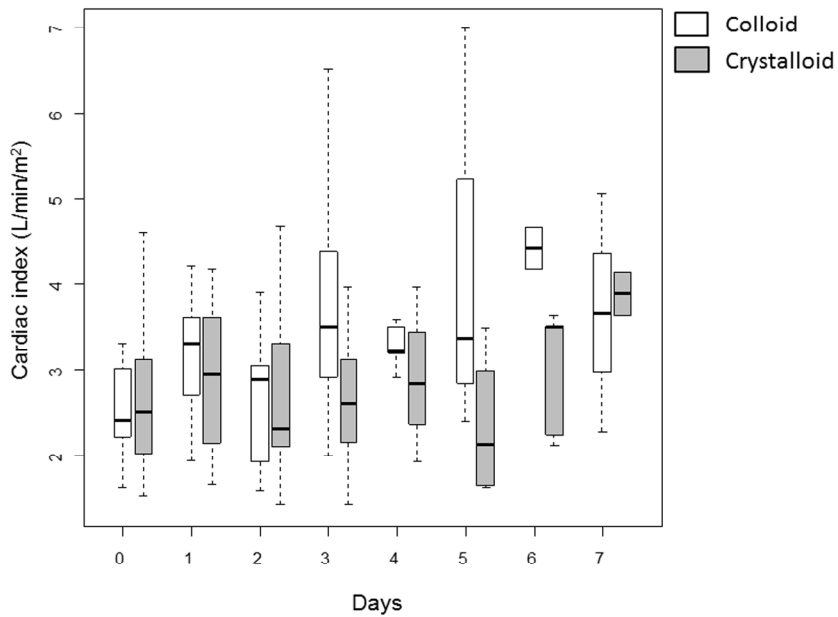


Figure2

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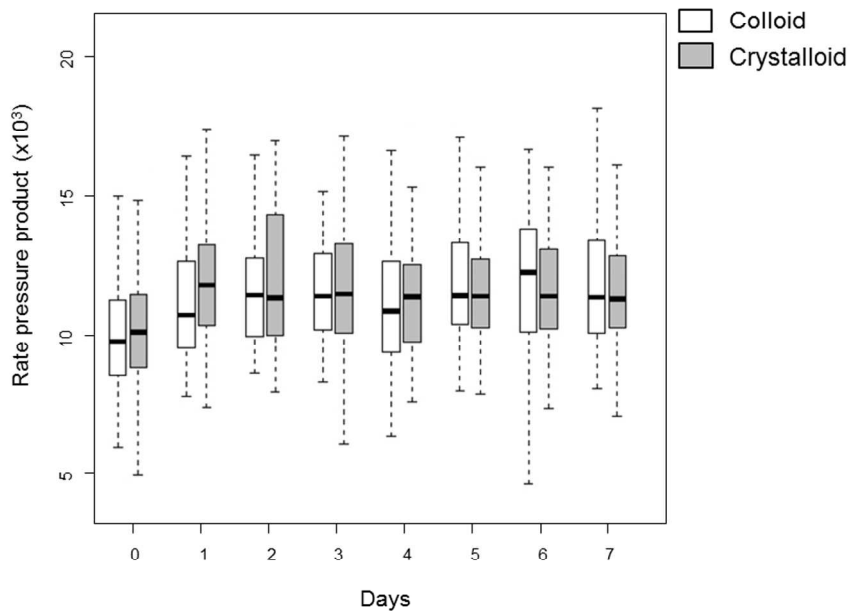


Figure3

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SUPPLEMENTAL DATA

Hemodynamic Response to Crystalloids or Colloids in Shock: An Exploratory Subgroup Analysis of the CRISTAL Trial.

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Table S1: Manifestations of acute hypovolemia at the time of inclusion

Variable	n = 220	Values Median (IQR) or %
Dizziness-n/total n (%)	43/90	47.8
Headache-n/total n (%)	10/82	12.2
Delirium-n/total n (%)	32/107	29.9
Thirst-n/total n (%)	19/78	24.4
Capillary refill time-seconds	29	3 [1 ;4]
Serum sodium-mmol/L	218	138 [135 ;141]
Protides-g/L	207	50 [40 ;59]
Albumin-g/L	114	22 [18 ;26.8]
Haematocrit-%	211	32 [28 ;37.5]
Blood urea nitrogen-mmol/L	219	0.56 [0.35 ;0.97]
Urinary output-ml/hour	207	46 [21.5 ;83]
Urinary sodium-mmol/L	99	42 [17 ;77]
Urinary urea nitrogen-mmol/L	91	8.4 [4.4 ;13.4]

Table S2: Type of fluid administered by treatment group

	Colloids n= 103	Crystalloids n= 117
Isotonic saline-n(%)	14 (13.6)	107 (91.4)
Ringer's lactate-n(%)	2 (1.9)	21 (17.9)
Gelatins -n(%)	37 (35.9)	2 (1.7)
Hydroxyethyl Starch-n(%)	81 (78.7)	8 (6.8)
Albumin-n(%)	20 (19.4)	22 (18.8)

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3 Supplemental Figures
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8 Figure S1: Box-plot showing systolic blood pressure distribution over the first seven
9 days following randomisation in both arms.
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12 The horizontal line in the box indicates the median value while the lines at the top
13 and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.
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19 Figure S2: Box-plot showing diastolic blood pressure distribution over the first seven
20 days following randomisation in both arms.
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23 The horizontal line in the box indicates the median value while the lines at the top
24 and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.
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30 Figure S3: Box-plot showing mean blood pressure distribution over the first seven
31 days following randomisation in both arms.
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34 The horizontal line in the box indicates the median value while the lines at the top
35 and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.
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41 Figure S4: Box-plot showing central venous pressure distribution over the first seven
42 days following randomisation in both arms.
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45 The horizontal line in the box indicates the median value while the lines at the top
46 and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.
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52 Figure S5: Box-plot showing pH distribution over the first seven days following
53 randomisation in both arms.
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3 The horizontal line in the box indicates the median value while the lines at the top
4 and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.
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10 Figure S6: Box-plot showing blood bicarbonate distribution over the first seven days
11 following randomisation in both arms.
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15 The horizontal line in the box indicates the median value while the lines at the top
16 and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.
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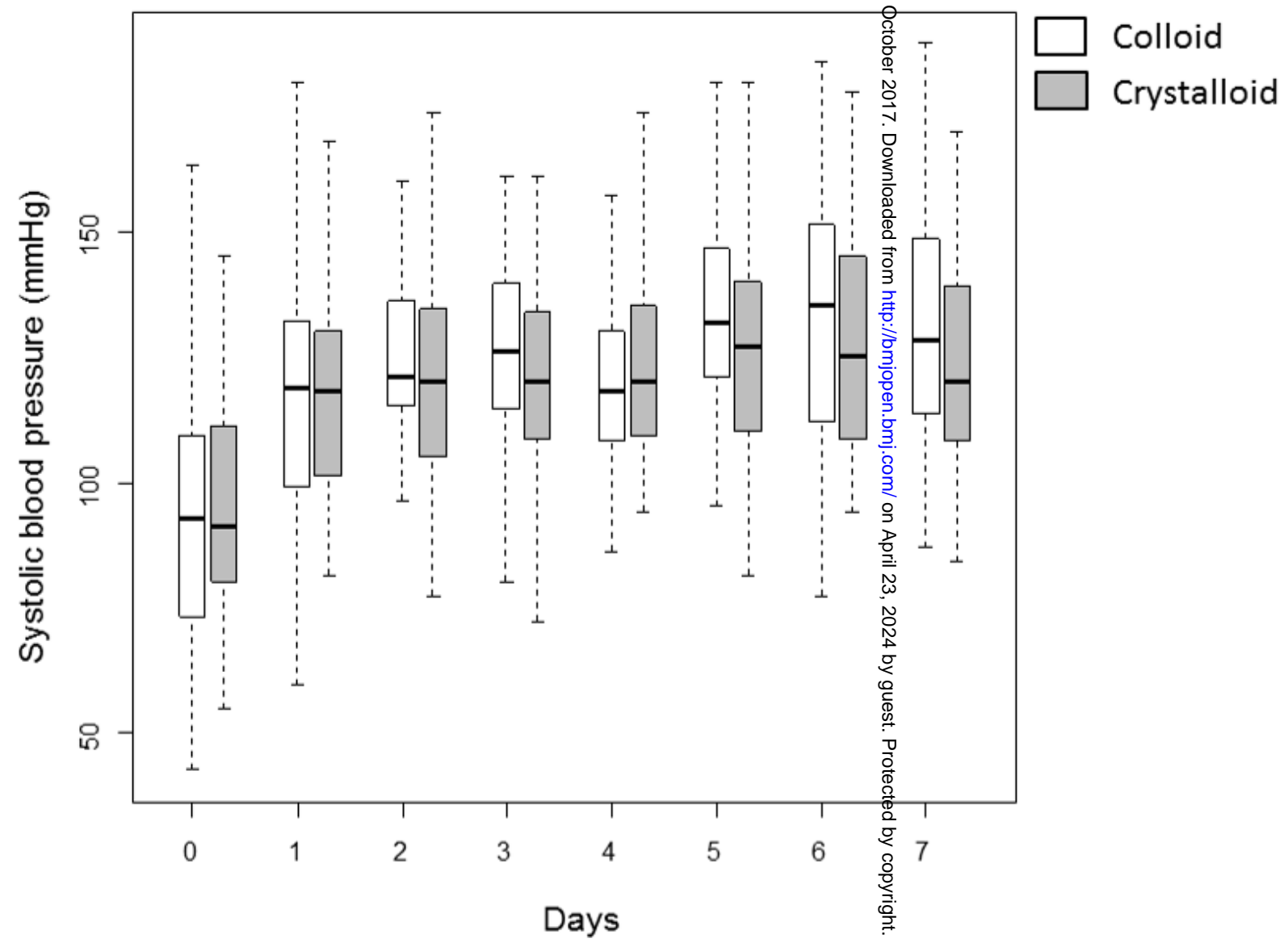
22 Figure S7: Box-plot showing arterial lactate distribution over the first seven days
23 following randomisation in both arms.
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27 The horizontal line in the box indicates the median value while the lines at the top
28 and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.
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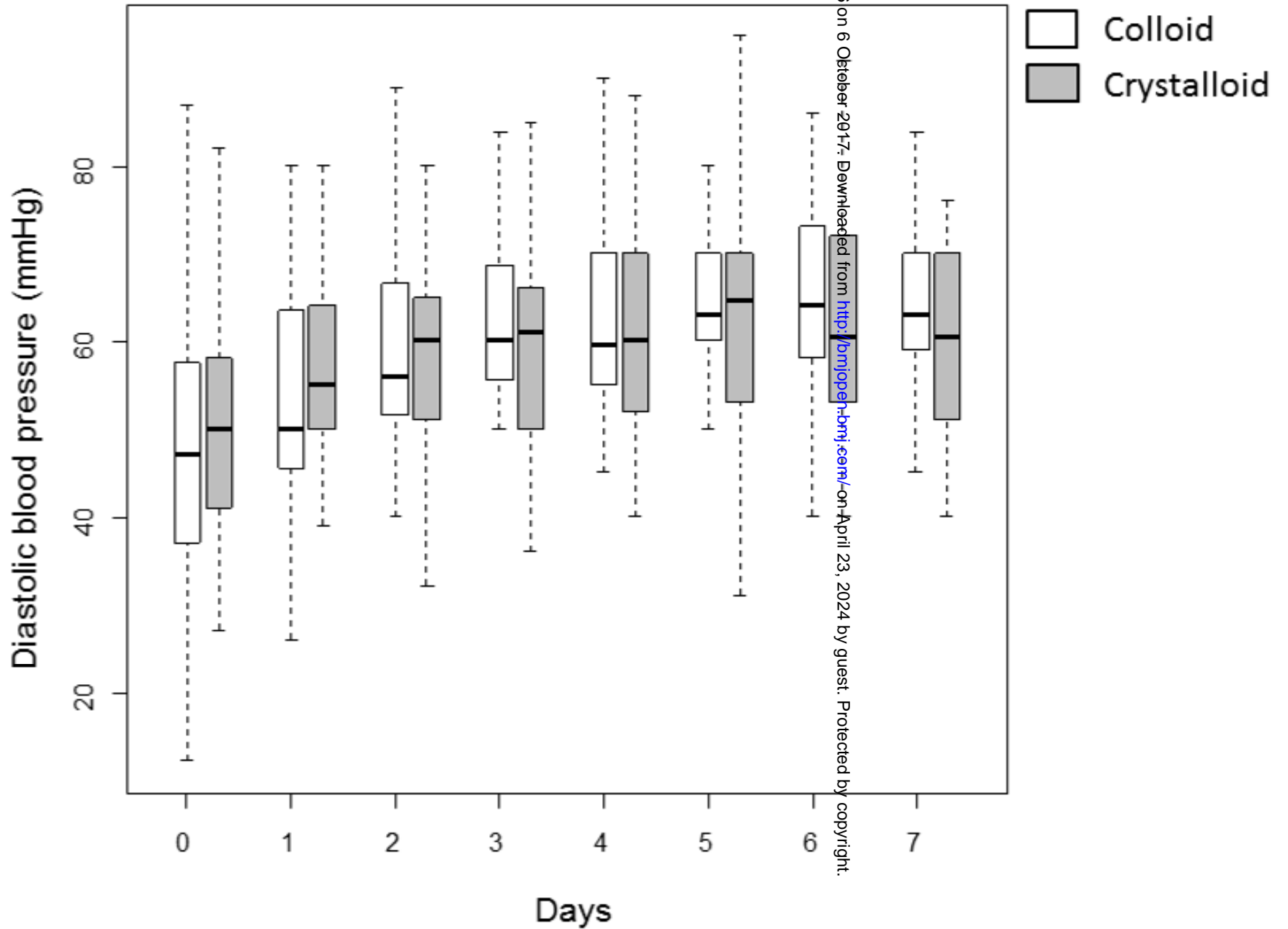
34 Figure S8: Box-plot showing daily urine output over the first seven days following
35 randomisation in both arms.
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39 The horizontal line in the box indicates the median value while the lines at the top
40 and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.
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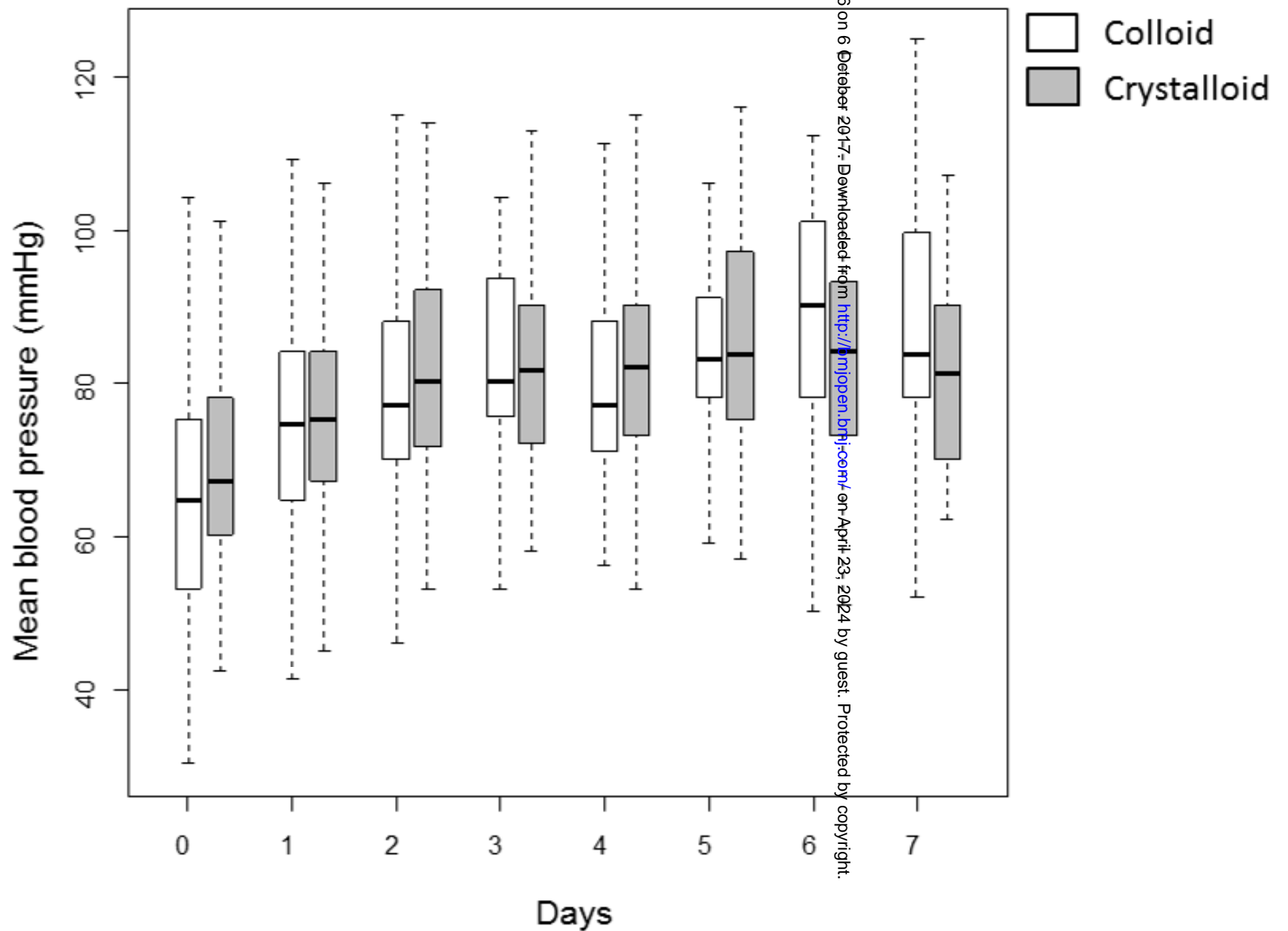
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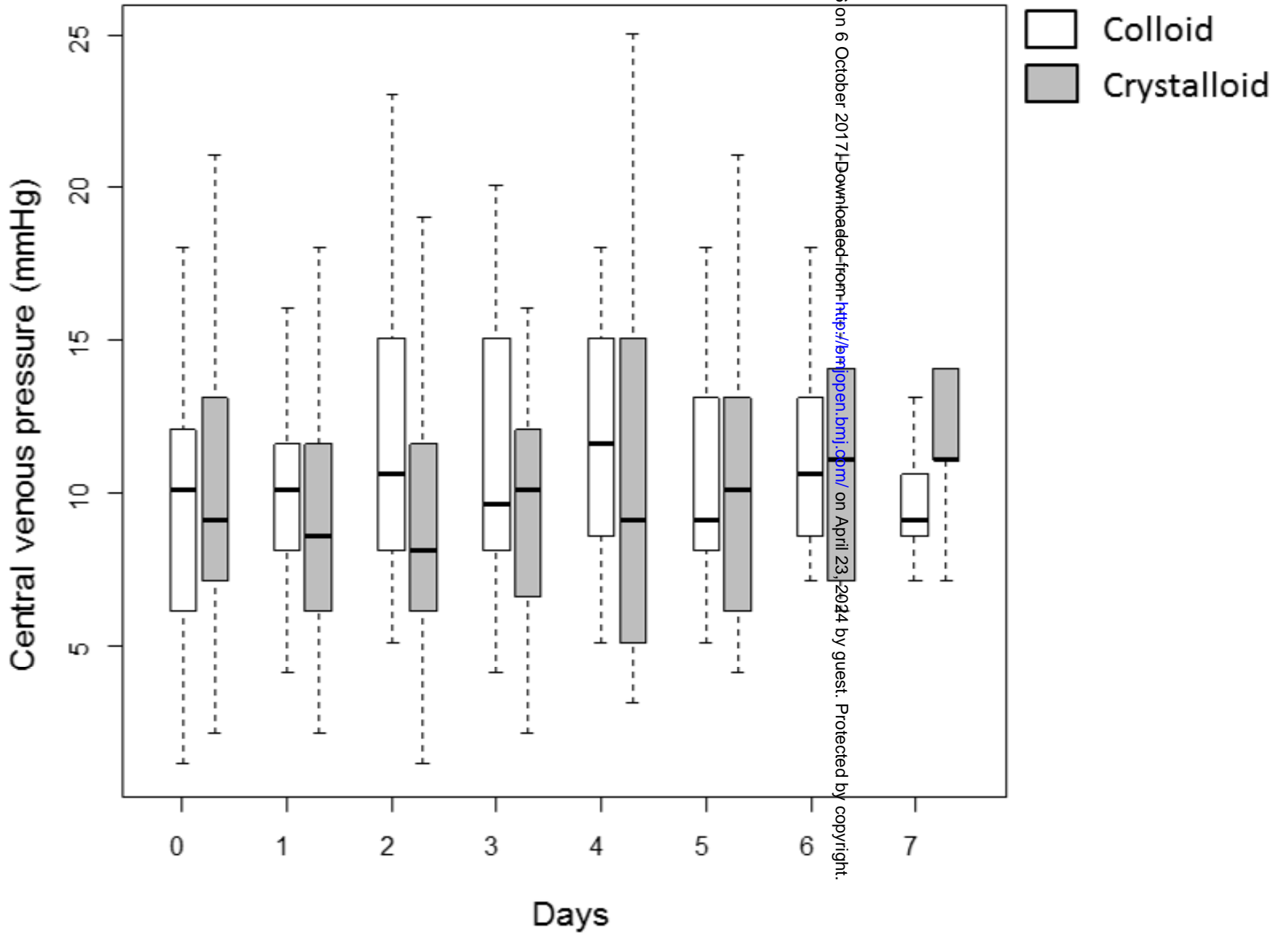
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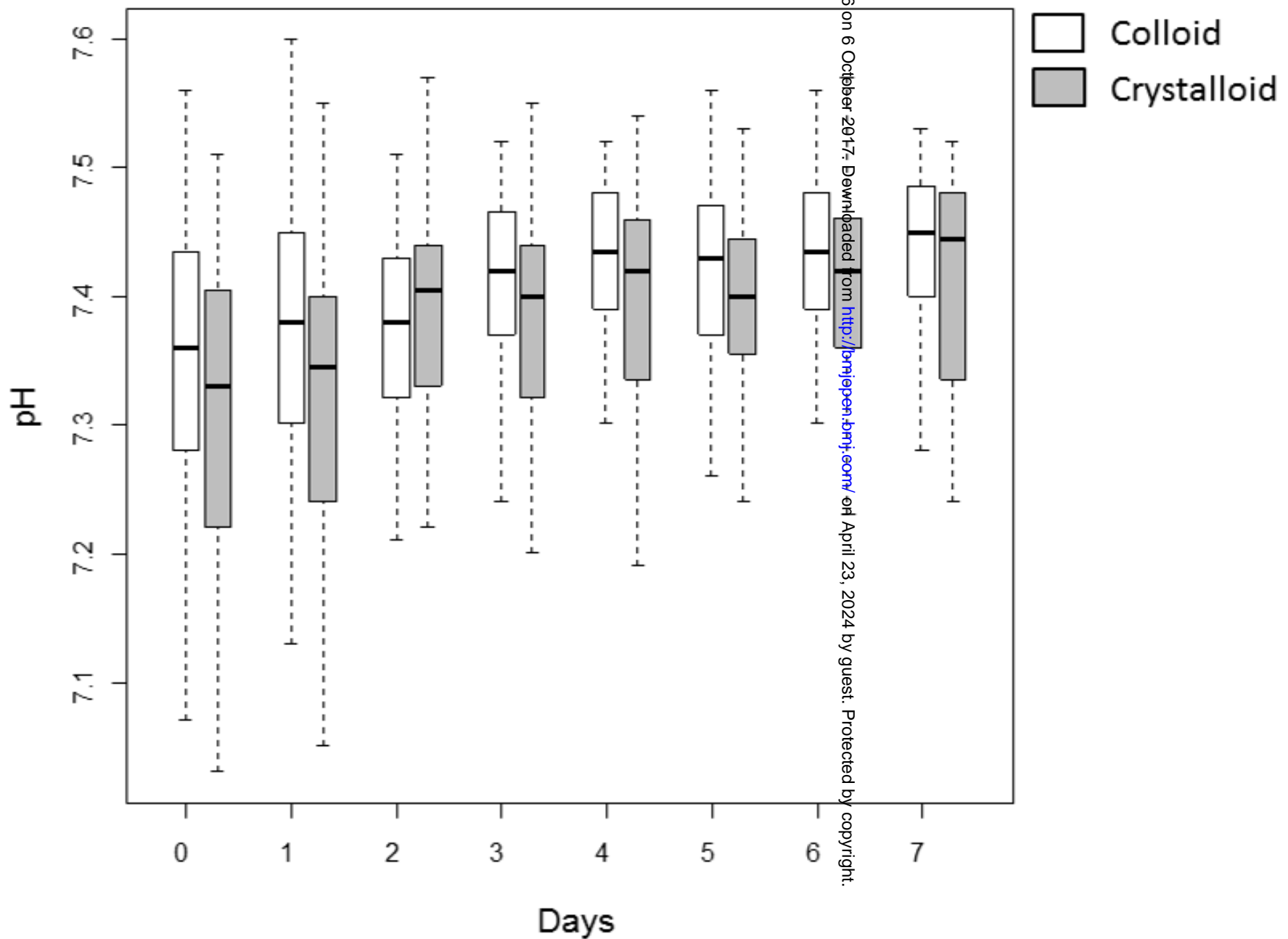
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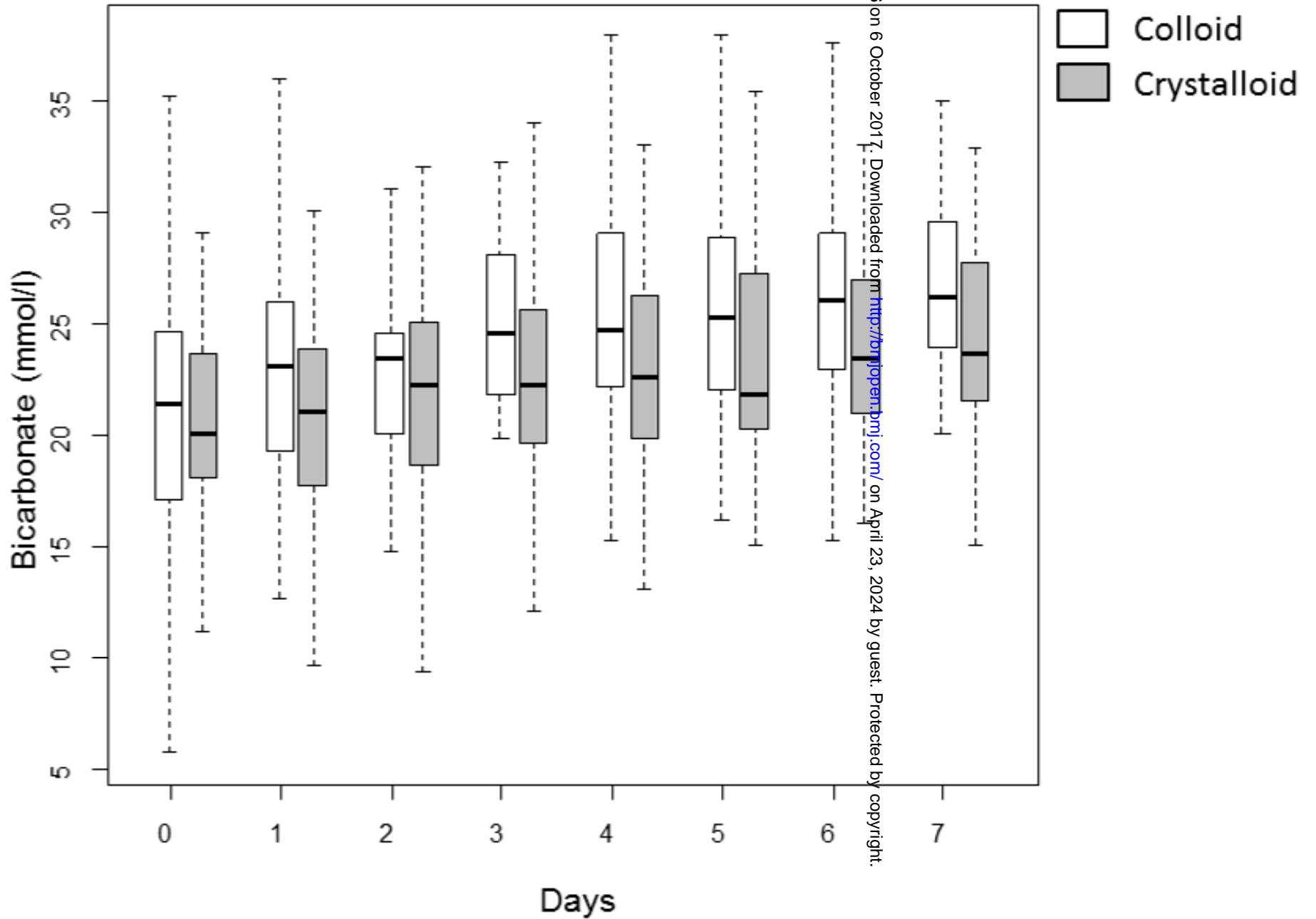
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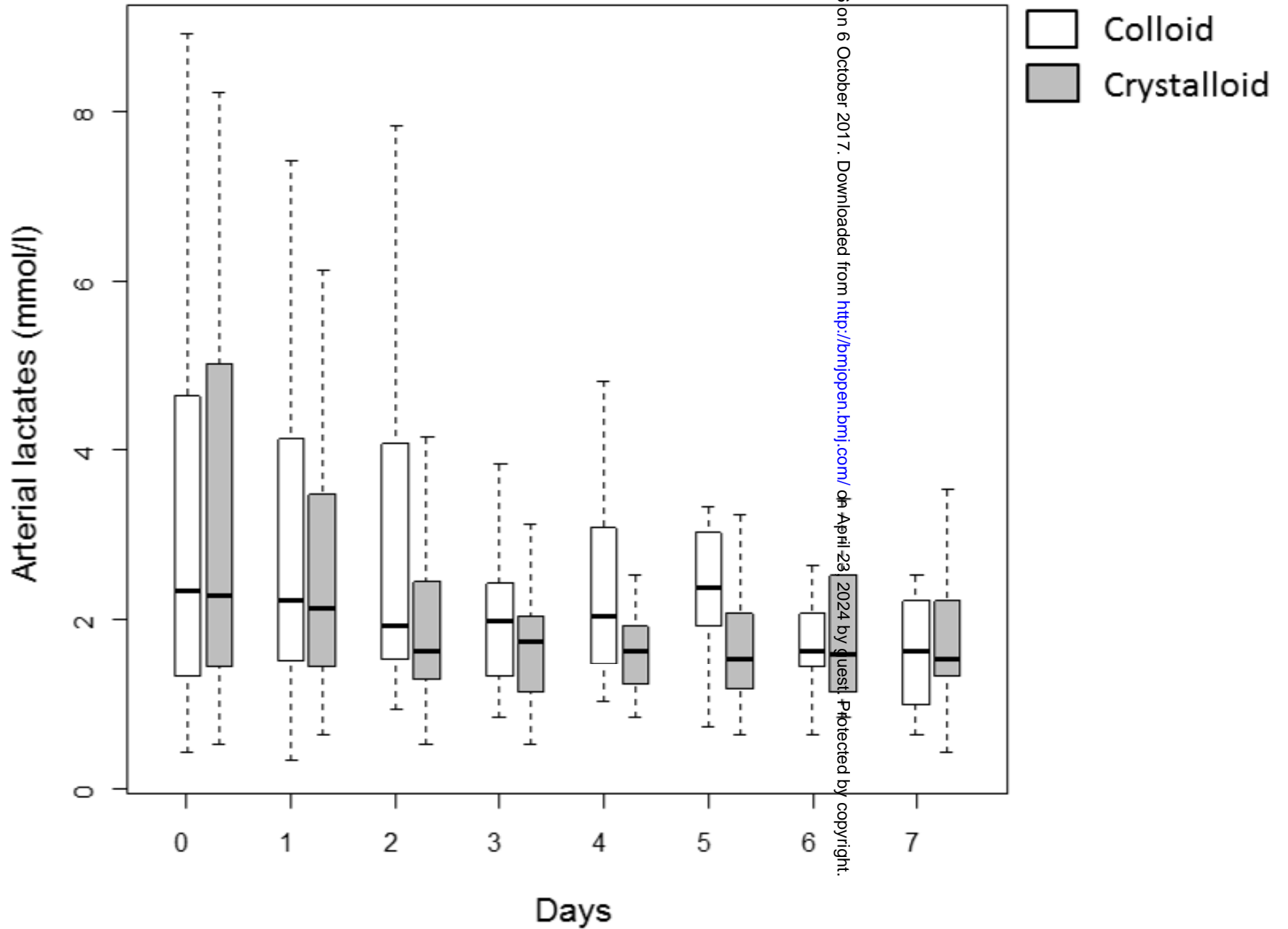


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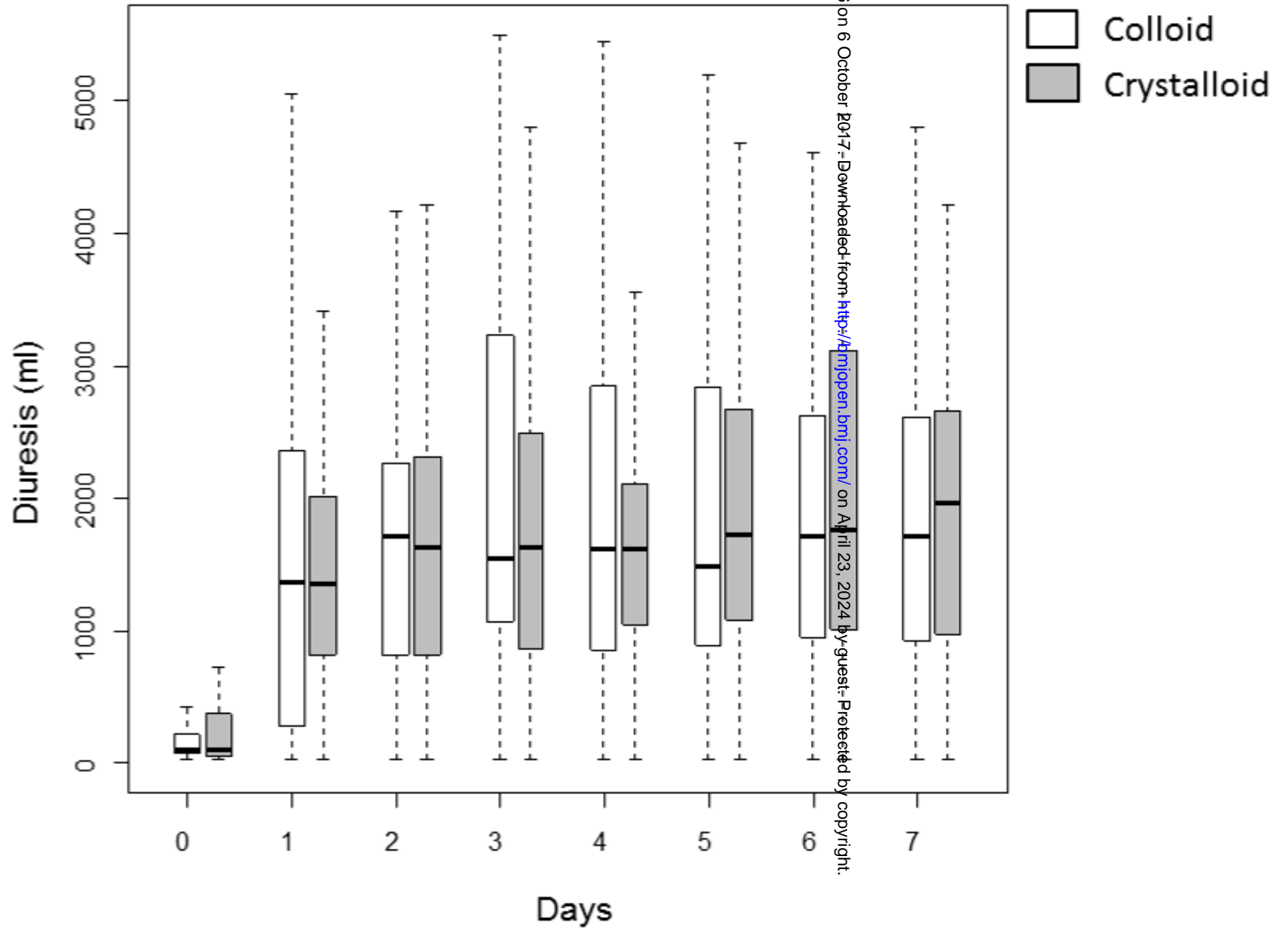


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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1	An Exploratory Subgroup Analysis of a Randomized Controlled Trial
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Current analysis included all patients who had a pulmonary artery catheter in place at randomisation. 220 patients (117 received crystalloids vs. 103 colloids) underwent pulmonary artery catheterization. Hemodynamic data were collected at the time of randomization and subsequently on days 1, 2, 3, 4, 5, 6, 7. Results: Median cumulative volume of fluid administered during the first 7 days was higher in the crystalloids group than in the colloids group (3500 [2000 ;6000] vs. 2500 [1000 ;4000] ml, $P = .01$). Patients in the colloids arm exhibited a lower heart rate over time compared to those allocated to the crystalloids arm ($P = .014$). There was no significant difference in cardiac index ($P = .053$), mean blood pressure ($P = .4$), arterial lactates ($P = .9$) or global SOFA score ($P = .3$) over time between arms.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	Fluid resuscitation is a cornerstone of the management of

hypovolemia. During hypovolemic shock, fluids restore intravascular volume, cardiac output, oxygen delivery and reverse peripheral hypoperfusion. Resuscitation fluids are divided into two distinct categories, crystalloids and colloids. On the one hand, crystalloids dilute the plasma protein content, reducing plasma oncotic pressure which may result in interstitial oedema. The most commonly used crystalloid, isotonic saline, induces hyperchloremic acidosis and acute kidney injury. On the other hand, colloids are composed of large molecules, increasing their vascular retention and are theoretically more effective for fluid resuscitation. However, the most commonly used colloid, starch, is associated with acute kidney injury, increased need for renal replacement therapy, accumulation in reticuloendothelial tissues, and increased requirements for blood products.

Objectives	3	State specific objectives, including any prespecified hypotheses	5	The current study aimed at assessing the hemodynamic effect of crystalloids vs. colloids in the CRISTAL participants monitored by pulmonary artery catheter.
Methods				
Study design	4	Present key elements of study design early in the paper	6	We included all patients who had a PAC in place as part of their routine management either prior to or within the first 24 hours of randomization.

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The 7 day time course of mean, systolic and diastolic blood pressure, central venous pressure, heart rate, cardiac index, and daily diuresis as well as the results of arterial blood gases were compared between arms. We then compared systolic, diastolic and mean pulmonary artery pressure and pulmonary artery occlusion pressure in both arms.

Setting 5 Describe the setting, locations, and relevant dates, including 6-8 periods of recruitment, exposure, follow-up, and data collection

The current study is a subgroup analysis of a randomized multicentre trial (CRISTAL, ClinicalTrials.gov NCT00318942), comparing the effect of crystalloid vs. colloid administration for fluid resuscitation in the intensive care unit on mortality at 28 days. REF Annane D, Siami S, Jaber S, *et al.* Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. *JAMA* 2013;310:1809–17.

Data collection
Demographic and general characteristics
The following data were prospectively collected at the time of randomization: age, gender, weight, source of admission, McCabe class and disability scale score. Severity scores including the Glasgow coma score, Simplified Acute Physiology Score II

(SAPS II) and the Sequential Organ Failure Assessment (SOFA) Score. Causes of acute hypovolemia were stratified in the initial trial as sepsis, trauma or other disorders. We collected a set of symptoms and biological signs of acute hypovolemia (supplemental table 1).

Hemodynamic variables

We prospectively measured, for as long as the PAC was in place or up to seven days (whichever occurred first), before randomisation and then once daily (by recording the first value reported in the medical file following the change of shift, i.e. typically around 08h00) the following hemodynamic data: heart rate, systolic, diastolic and mean blood pressure, central venous pressure (CVP), systolic, diastolic and mean pulmonary artery pressure, pulmonary artery occlusion pressure (PAOP), cardiac index, and urinary output. Additionally, mean blood pressure was recorded hourly following the first 24 hours after randomisation. We calculated, using standard formulas, the product of the heart rate and systolic blood pressure (or rate-pressure product, RPP), a marker of myocardial perfusion requirement, systemic and pulmonary vascular resistances, stroke volume index, left and

right ventricular stroke work index. Laboratory values included arterial pH, bicarbonate, lactate and SvO₂. Finally, to compare colloids to crystalloids in reaching the hemodynamic targets of the 6-hour bundles of the Surviving Sepsis campaign, we collected these same variables, six hours after randomisation.

Other variables

We collected before randomisation and daily up to seven days post randomization, the SOFA score and the cumulative volume of administered fluids and throughout the trial the occurrence of the main interventions including, packed red blood cell transfusion, the administration of vasopressors, mechanical ventilation, or renal replacement therapy.

Participants	6	<p>(a) <i>Cohort study</i>—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</p> <p><i>Case-control study</i>—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls</p> <p><i>Cross-sectional study</i>—Give the eligibility criteria, and the sources and methods of selection of participants</p> <p>(b) <i>Cohort study</i>—For matched studies, give matching criteria and number of exposed and unexposed</p> <p><i>Case-control study</i>—For matched studies, give matching criteria and the number of controls per case</p>	6	<p>For the current ancillary study, among the CRISTAL population, we included all patients who had a PAC in place as part of their routine management either prior to or within the first 24 hours of randomization.</p>
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Variables	7 Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8	<p>The following data were prospectively collected at the time of randomization: age, gender, weight, source of admission, McCabe class and disability scale score. Severity scores including the Glasgow coma score, Simplified Acute Physiology Score II (SAPS II) and the Sequential Organ Failure Assessment (SOFA) Score. Causes of acute hypovolemia were stratified in the initial trial as sepsis, trauma or other disorders. We collected a set of symptoms and biological signs of acute hypovolemia (supplemental table 1).</p> <p>Hemodynamic variables</p> <p>We prospectively measured, for as long as the PAC was in place or up to seven days (whichever occurred first), before randomisation and then once daily (by recording the first value reported in the medical file following the change of shift, i.e. typically around 08h00) the following hemodynamic data: heart rate, systolic, diastolic and mean blood pressure, central venous pressure (CVP), systolic, diastolic and mean pulmonary artery pressure, pulmonary artery occlusion pressure (PAOP), cardiac index, and urinary output. Additionally, mean blood pressure was recorded hourly following the first 24 hours after randomisation.</p>
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We calculated, using standard formulas, the product of the heart rate and systolic blood pressure (or rate-pressure product, RPP), a marker of myocardial perfusion requirement, systemic and pulmonary vascular resistances, stroke volume index, left and right ventricular stroke work index. Laboratory values included arterial pH, bicarbonate, lactate and SvO₂. Finally, to compare colloids to crystalloids in reaching the hemodynamic targets of the 6-hour bundles of the Surviving Sepsis campaign, we collected these same variables, six hours after randomisation.

Other variables

We collected before randomisation and daily up to seven days post randomization, the SOFA score and the cumulative volume of administered fluids and throughout the trial the occurrence of the main interventions including, packed red blood cell transfusion, the administration of vasopressors, mechanical ventilation, or renal replacement therapy.

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8	Demographic and general characteristics The following data were prospectively collected at the time of randomization: age, gender, weight, source of admission, McCabe class and disability scale score. Severity scores including the
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Glasgow coma score, Simplified Acute Physiology Score II (SAPS II) and the Sequential Organ Failure Assessment (SOFA) Score. Causes of acute hypovolemia were stratified in the initial trial as sepsis, trauma or other disorders. We collected a set of symptoms and biological signs of acute hypovolemia (supplemental table 1).

Hemodynamic variables

We prospectively measured, for as long as the PAC was in place or up to seven days (whichever occurred first), before randomisation and then once daily (by recording the first value reported in the medical file following the change of shift, i.e. typically around 08h00) the following hemodynamic data: heart rate, systolic, diastolic and mean blood pressure, central venous pressure (CVP), systolic, diastolic and mean pulmonary artery pressure, pulmonary artery occlusion pressure (PAOP), cardiac index, and urinary output. Additionally, mean blood pressure was recorded hourly following the first 24 hours after randomisation. We calculated, using standard formulas, the product of the heart rate and systolic blood pressure (or rate-pressure product, RPP), a marker of myocardial perfusion requirement, systemic and

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pulmonary vascular resistances, stroke volume index, left and right ventricular stroke work index. Laboratory values included arterial pH, bicarbonate, lactate and SvO₂. Finally, to compare colloids to crystalloids in reaching the hemodynamic targets of the 6-hour bundles of the Surviving Sepsis campaign, we collected these same variables, six hours after randomisation.

Other variables
We collected before randomisation and daily up to seven days post randomization, the SOFA score and the cumulative volume of administered fluids and throughout the trial the occurrence of the main interventions including, packed red blood cell transfusion, the administration of vasopressors, mechanical ventilation, or renal replacement therapy.

Bias	9	Describe any efforts to address potential sources of bias	6,7,8	We included all patients who had a PAC in place as part of their routine management Causes of acute hypovolemia were stratified in the initial trial as sepsis, trauma or other disorders. We report on all statistical analysis done.
Study size	10	Explain how the study size was arrived at	6	For the current ancillary study, among the CRISTAL population, we included all patients who had a PAC in place as part of their routine management either prior to or within the first 24 hours of randomization.

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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8	<p>Quantitative variables are expressed as median [interquartile range]</p> <p>Mixed effects models, which are appropriate for clustered and dependent data, were used to study the relationship between treatment arms. The area under the curve of mean blood pressure was estimated for each individual, over the first 24 hours, using polynomial integration and compared using the Wilcoxon rank sum test. Number of days alive without vasopressor therapy was compared using the Wilcoxon rank sum test. The proportion of patients reversing signs of hypoperfusion (mean blood pressure (MAP) \geq 65 mm Hg, urine output \geq 0.5 mL/kg/h, CVP between 8 and 12 mmHg and SvO₂ \geq 65%, within the first 6 hours of resuscitation) in the sepsis subgroup was compared using the exact Fisher test.</p> <p>²⁶ Complete cases analysis was undertaken.</p>
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8	<p>Quantitative variables are expressed as median [interquartile range] and categorical variables as number (percentage). The 7 day time course of mean, systolic and diastolic blood pressure, central venous pressure, heart rate, cardiac index, and daily diuresis as well as the results of arterial blood gases</p>

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were compared between arms. We then compared systolic, diastolic and mean pulmonary artery pressure and pulmonary artery occlusion pressure in both arms. In order to further explore differences between arms, we calculated the rate pressure product as well as the various indexes derived from the use of the PAC. Mixed effects models, which are appropriate for clustered and dependent data, were used to study the relationship between treatment arms and the time course of hemodynamic variables as well as the global SOFA score.²⁵ The area under the curve of mean blood pressure was estimated for each individual, over the first 24 hours, using polynomial integration and compared using the Wilcoxon rank sum test. The proportion of patients reversing signs of hypoperfusion (mean blood pressure (MAP) \geq 65 mm Hg, urine output \geq 0.5 mL/kg/h, CVP between 8 and 12 mmHg and SvO₂ \geq 65%, within the first 6 hours of resuscitation) in the sepsis subgroup was compared using the exact Fisher test.²⁶ Complete cases analysis was undertaken. Since the current analysis was deemed exploratory and since we report on all statistical analysis done, no correction for multiples testing

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was deemed necessary. Statistical analyses were performed using SAS 9.3 (SAS Inc, Cary, NC) and R 2.13.0 (<http://www.R-project.org/>) software. Tests were two sided. $P < 0.05$ was considered significant.

(b) Describe any methods used to examine subgroups and interactions

Mixed effects models, which are appropriate for clustered and dependent data, were used to study the relationship between treatment arms and the time course of hemodynamic variables as well as the global SOFA score.

(c) Explain how missing data were addressed

8

Complete cases analysis was undertaken.

(d) *Cohort study*—If applicable, explain how loss to follow-up was addressed

8

Complete cases analysis was undertaken.

Case-control study—If applicable, explain how matching of cases and controls was addressed

Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy

(e) Describe any sensitivity analyses

Mixed effects models, which are appropriate for clustered and dependent data, were used to study the relationship between treatment arms and the time course of hemodynamic variables as well as the global SOFA score.

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4,10	The CRISTAL trial included 2857 subjects. Among the CRISTAL population, 220 subjects had a PAC in place as part of their routine management, of which 103 received colloids and 117 crystalloids, accounting for a total of 645 catheter-days. All patients were analysed.
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		(b) Give reasons for non-participation at each stage		The CRISTAL trial included 2857 subjects. Among the CRISTAL population, 220 subjects had a PAC in place as part of their routine management, of which 103 received colloids and 117 crystalloids, accounting for a total of 645 catheter-days. All patients were analysed.
		(c) Consider use of a flow diagram		NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	17, 18	Table1 and Table 2
		(b) Indicate number of participants with missing data for each variable of interest	18	Table 2
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	10	We collected before randomisation and daily up to seven days post randomization. Accounting for a total of 645 catheter-days.
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	10,11	Median cumulative volume of fluid administered during the first 7 days in the ICU was higher in the crystalloids than in the colloids arm (3500 [2000 ;6000] vs. 2500 [1000 ;4000] ml respectively ($P = .01$)). Supplemental table 2 displays the distribution of fluid types within each study arm. During the first 24 hours following randomisation, mean blood pressure did not significantly differ between treatment arm (mean area under the curve 78 [68 ;84] for colloids vs. 77 [70 ;84] mmHg/h for crystalloids ($P = .6$)). The heart rate was lower in the colloids than in the crystalloids group ($P = .014$) (Figure 1). Systolic, diastolic and mean blood pressure did not

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significantly differ between arms ($P = .6$, $P = .2$ and $P = .4$, respectively) (supplemental Figures 1, 2 and 3). Cardiac index, although the difference was not statistically significant ($P = .053$), was higher in colloids treated patients compared to those treated with crystalloids (Figure 2). Central venous pressure did not differ between both arms ($P = .9$) (supplemental Figure 4). Subjects in the colloids arm exhibited a lower rate-pressure product, ($P = .036$) (Figure 3). Arterial pH, arterial levels of bicarbonate and lactate did not differ between groups ($P = .3$, $P = .3$ and $P = .9$, respectively) (supplemental Figures 5, 6 and 7). Mixed venous oxygen saturation, daily urine output (supplemental Figure 8), and the SOFA score did not differ between both arms ($P = .9$, $P = .15$ and $P = .3$, respectively). Hemodynamic stability was reached through a similar use of vasopressors (Table 3). Other relevant outcomes did not significantly differ between both groups. Isotonic saline solutions and hydroxyl starches were the most common types of administered fluids, among, respectively crystalloids and colloids groups. We therefore compared the overall time-course of hemodynamic parameters between

isotonic saline treated patients and those treated with hydroxyethyl starches. Treatment with hydroxyethyl starches was associated with a lower heart rate ($P = .023$), and a lower rate pressure product ($P = .042$) compared to isotonic saline.

Case-control study—Report numbers in each exposure category, or summary measures of exposure

Cross-sectional study—Report numbers of outcome events or summary measures

Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10	Median cumulative volume of fluid administered during the first 7 days in the ICU was higher in the colloids than in the colloids arm (3500 [2000 ;6000] vs. 2500 [1000 ;4000] ml respectively ($P = .01$)). Supplemental table 2 displays the distribution of fluid types within each study arm. During the first 24 hours following randomisation, mean blood pressure did not significantly differ between treatment arm (mean area under the curve 78 [68 ;84] for colloids vs. 77 [70 ;84] mmHg/h for crystalloids ($P = .6$)). The heart rate was lower in the colloids than in the crystalloids group ($P = .014$) (Figure 1). Systolic, diastolic and mean blood pressure did not significantly differ between arms ($P = .6$, $P = .2$ and $P = .4$, respectively) (supplemental Figures 1, 2 and 3). Cardiac
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index, although the difference was not statistically significant ($P = .053$), was higher in colloids treated patients compared to those treated with crystalloids (Figure 2). Central venous pressure did not differ between both arms ($P = .9$) (supplemental Figure 4). Subjects in the colloids arm exhibited a lower rate-pressure product, ($P = .036$) (Figure 3). Arterial pH, arterial levels of bicarbonate and lactate did not differ between groups ($P = .3$, $P = .3$ and $P = .9$, respectively) (supplemental Figures 5, 6 and 7). Mixed venous oxygen saturation, daily urine output (supplemental Figure 8), and the SOFA score did not differ between both arms ($P = .9$, $P = .15$ and $P = .3$, respectively). Hemodynamic stability was reached through a similar use of vasopressors (Table 3). Other relevant outcomes did not significantly differ between both groups.

Isotonic saline solutions and hydroxyl starches were the most common types of administered fluids, among, respectively crystalloids and colloids groups. We therefore compared the overall time-course of hemodynamic parameters between isotonic saline treated patients and those treated with hydroxyethyl starches. Treatment with hydroxyethyl starches

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was associated with a lower heart rate ($P = .023$), and a lower rate pressure product ($P = .042$) compared to isotonic saline.

(b) Report category boundaries when continuous variables were categorized NA

(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period NA

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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		NA
Discussion				
Key results	18	Summarise key results with reference to study objectives	11	We found that colloids achieved broadly similar resuscitation goals to crystalloids using lower volumes of administered fluids. Additionally, colloids may exhibit a favourable impact on heart rate and rate-pressure product. Colloids did not affect any other hemodynamic endpoints. We found, in patients with sepsis, no evidence for a superiority of colloids over crystalloids in achieving hemodynamic targets of the 6-hour bundle of the Surviving Sepsis Campaign.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14	Our study has several limitations. First, our subgroup accounts for less than ten percent of the global CRISTAL trial population; the small size of our subgroup is related to a steady decline in the use of the pulmonary artery catheter during the CRISTAL trial, amidst reports that the use of pulmonary artery catheter does not alter outcome in ICU patients, and increased availability of less invasive hemodynamic monitoring tools. Moreover, some selection bias may have been introduced, due to the fact that PA catheterization was not performed within the 24 hours of randomization in about one fourth of the sample. Complete case

				analyses performed on available measurements further assumes that missing mechanisms were unrelated to patient status. Finally, some inflation of type I error rate associated with the number of tests undertaken is possible, meaning that interpretation of results should be exploratory.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13	The implication is that from a hemodynamic point of view, fluid resuscitation with colloids or crystalloids is broadly equivalent – maybe with a slight advantage for colloids-although the price of resuscitation using crystalloids would be an increase in the total volume of administered fluids.
Generalisability	21	Discuss the generalisability (external validity) of the study results	13	The implication is that from a hemodynamic point of view, fluid resuscitation with colloids or crystalloids is broadly equivalent – maybe with a slight advantage for colloids-although the price of resuscitation using crystalloids would be an increase in the total volume of administered fluids.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16	The CRISTAL study was funded by 2001 and 2010 grants (AOM 01 020) from the French Ministry of Health.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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