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

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Keywords: Fluid resuscitation; Crystalloid; Colloid; Pulmonary artery catheter; Intensive Care Unit (ICU).

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Abstract

Objective: To compare the hemodynamic effect of crystalloids and colloids during acute severe hypovolemic shock.

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

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

Participants: 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.

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

Outcome measures: 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.

Conclusions: In the CRISTAL trial, patients monitored by a pulmonary artery catheter achieved broadly similar hemodynamic goals, using lower volumes of colloids than crystalloids. The heart rate was lower in the colloids arm.

Strengths and limitations of this study

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

Introduction

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

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

trials comparing a single colloid to a single crystalloid. [13-15] However, mortality by 90 days was significantly lower in the colloids arm that in the crystalloids arm (30.7% vs. 34.2%). This finding was deemed exploratory. Additionally, the number of days alive at 7 and 28 days without vasopressor therapy was higher in the colloids than in the crystalloids arm. We sought to compare the effect of crystalloids to that of colloids on hemodynamic parameters during hypovolemic shock. The pulmonary artery catheter (PAC) remains the only method to provide a comprehensive, reliable and reproducible measure of hemodynamic data. Contrary to other methods, the PAC can determine pulmonary artery pressures, pulmonary artery occlusion pressure as well as derived variables. [18] The current study is aimed at assessing the hemodynamic effect of crystalloids or colloids in the group of patients monitored by pulmonary artery catheter.

Materials and Methods

1) Study setting and patients

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

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.

2) 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 [19] and disability scale score. [20] Severity scores included the Glasgow coma score, [21] Simplified Acute Physiology Score II (SAPS II) [22] and the Sequential Organ Failure Assessment (SOFA) Score. [23]

Causes of acute hypovolemia including sepsis, trauma and other disorders were recorded. We collected a set of symptoms of acute hypovolemia (see supplemental table 1).

Hemodynamic variables

We prospectively measured as long as the PAC was in place or up to seven days (pending which occurred first), at baseline and once daily (i.e. the first value reported in the medical file following the change of shift, typically around 08h00) heart rate (HR, bpm), systolic (SBP, mmHg), diastolic (DBP, mmHg) and mean blood (MBP, mmHg) pressure, central venous pressure (CVP, mmHg), systolic (PSBP, mmHg), diastolic (PDBP, mmHg) and mean pulmonary artery (PMBP, mmHg) pressure, pulmonary artery occlusion pressure (PAOP, mmHg), cardiac index (L/min/m^2), and urinary output (ml/kg/hour). We calculated, using standard formulas, the product of heart rate and systolic blood pressure (or rate-pressure product, RPP), a marker of myocardial perfusion requirement, and systemic (SVR, dyn.s/cm^5) and pulmonary (PVR, dyn.s/cm^5) vascular resistances, stroke volume index (SVI, ml/m^2), left (LVSWI, g.m/m²) and right (RVSWI, g.m/m²) ventricular stroke work index. Laboratory values included arterial pH, levels of bicarbonate (mmol/l), lactate (mmol/l) and SvO_2 (%).

Additionally, in order to compare colloids to crystalloids in achieving the hemodynamic targets of the 6-hour bundles of the Surviving Sepsis campaign, we collected these same variables, six hours after randomisation. [24]

Other variables

We collected at baseline and daily up to seven days post randomization, the SOFA score and main interventions including the cumulative volume of administered fluids,

blood products transfusion, type and dose of vasopressors, mechanical ventilation, and renal replacement therapy.

3) Statistical analysis

Quantitative variables are expressed as median [interquartile range] and categorical variables as number (percentage). The time course over a 7 day period of mean, systolic and diastolic blood pressure, central venous pressure, heart rate, cardiac index, results of arterial blood gases and daily diuresis 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 both arms, we calculated the rate pressure product as well as the various indexes derived from the use of the PAC and compared them between arms. 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) ≥ 65 mm Hg, urine output ≥ 0.5 mL/kg/h, CVP between 8 and 12 mmHg and SvO_2 ≥ 65%, within the first 6 hours of resuscitation) in the sepsis subgroup was compared using the exact Fisher test. [26] We undertook complete cases analysis. Since the current analysis was deemed exploratory and since we report on all statistical analysis done, no correction for multiples testing 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.

Results

Patients

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. PAC was placed mainly within 24 hours of randomization (n = 163; 74%), either before (n = 79) or within 24 hours of randomization (n = 84). Characteristics of the subgroup of PAC-monitored patients were similar to those of the whole population of the CRISTAL study, regarding age, gender and initial severity scores (Table 1). 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.

Treatments effects on hemodynamic variables

Hemodynamic variables at the time of randomisation are described in Table 2. Patients receiving colloids exhibited lower heart rate compared to those receiving crystalloids (*P* = .014) (Figure 1). Systolic, diastolic and mean blood pressure did not differ significantly 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 (respectively *P* = .3, *P*

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

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.

Sepsis subgroup

Among PAC-monitored patients, 108 subjects had sepsis, and 52 and 56 were allocated respectively to colloids and crystalloids. We compared the number of patients achieving mean blood pressure levels ≥ 65 mm Hg and urine output ≥ 0.5 mL/kg/h within the first 6 hours. [24] A total of 35/51 (69 %) patients in the crystalloids arm achieved MAP ≥ 65 mm Hg after 6 hours vs. 31/47 (66%) in the colloids arm (*P* = .8); 25/38 (66%) patients in the crystalloids arm achieved urine output ≥ 0.5 mL/kg/h after 6 hours vs. 17/28 (61%) in the colloids arm (*P* = .8). Limited data precluded the analysis of CVP and SvO_2 values during the first six hours following randomisation.

Discussion

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. [24] Tachycardia may increase myocardial work, with subsequent excessive myocardial energy expenditure, [27] and worse outcomes in the critically ill. [28 29]

The efficacy of fluid resuscitation is determined by the capacity of administered fluids to remain in the intravascular space. [1] The superior oncotic pressure of colloids is associated with increased intravascular expansion capacity compared to crystalloids. In order to achieve similar resuscitation goals, compared to colloids, between 20 and 50% more volume of crystalloids should be administered. [12 13 17 30] Inflammatory states such as those observed during critical illness are usually associated with endothelial dysfunction, leading to interstitial oedema. Reducing volumes of administered fluids may be of clinical benefit and a negative fluid balance improved outcome in ARDS, a frequent complication of sepsis. [31 32] By contrast, in septic shock, a positive fluid balance has been associated with a worse outcome. [33] However, colloid administration may be unsafe. Starches, the most commonly used colloid, may be associated with increased risk of acute kidney injury and increased need for renal replacement therapy, both in the general ICU population and in sepsis. [12 13 16] The use of starches has now been restricted in the ICU in Europe and the US. [34 35]

Our findings are similar to those of several of the other major trials. Most trials compared one type of colloid to one type of crystalloid. The SAFE study compared 4% albumin to 9‰ saline in critically ill patients. [14] Albumin administration was associated with a statistically significant lower heart rate on the first day of treatment, although the difference was small. The ALBIOS study compared 20% albumin (titrated to achieve a serum albumin concentration of over 30 g/L) to 9‰ saline in patients suffering from severe sepsis. [15] Over the first 7 days after randomization, patients in the albumin arm had lower heart rate and shorter duration of vasopressor therapy. The CHEST trial, compared hydroxyethyl starches to 9‰ saline for fluid resuscitation in critically ill patients. [13] Among the various hemodynamic targets, higher central venous pressure over the first four days following randomization was the only statistically significant difference between hydroxyethyl starches and 9‰ saline treated patients. The authors of the CHEST study concluded that crystalloids were as effective as colloids for initial resuscitation. The Scandinavian 6S trial randomized patients with severe sepsis to receive either hydroxyethyl starches or Ringer's acetate. [12] The hemodynamic targets were similar between both arms over the first 24 hours after randomization. Of note, subjects enrolled in both CHEST and 6S studies were enrolled up to 24 hours after their admission to the ICU, hence after the initial resuscitation phase.

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.

Conclusion: CRISTAL trial research participants with severe acute hypovolemic shock and monitored by a pulmonary artery catheter had lower heart rate when treated with colloids compared to crystalloids. As compared to colloids, crystalloids were as effective, though requiring higher volume, in reaching all other hemodynamic endpoints.

Authors' Contributions: NH, SC, DA were involved in study concept and design; NH, SE, SJ, A-SD, JC, XF, AK, J-LT, JF, NA, MD, CM acquired the data; SC was involved in the statistical analysis; NH, SC, DA were involved in analysis and interpretation of data; NH and DA drafted the manuscript; all authors critically revised the manuscript for important intellectual content; DA was involved in study supervision. All authors read and approved the final manuscript.

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Competing interests: None declared.

Data sharing statement: Individual data are available by contacting DA at djillali.annane@aphp.fr

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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)

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

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

Table 2. Physiological values at baseline according to randomisation

	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]

SvO_2: mixed venous oxygen saturation

Figure Legend

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

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

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

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

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

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

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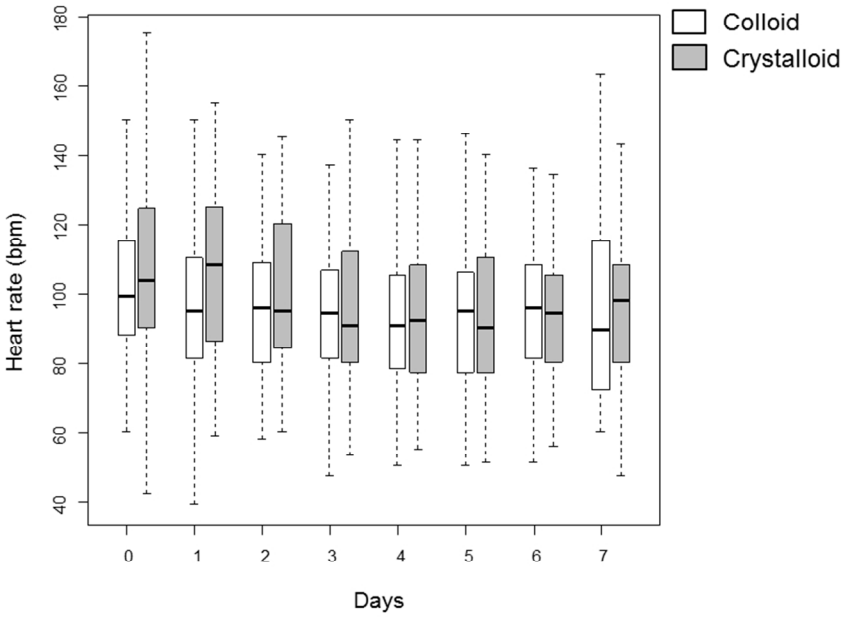

Figure 1

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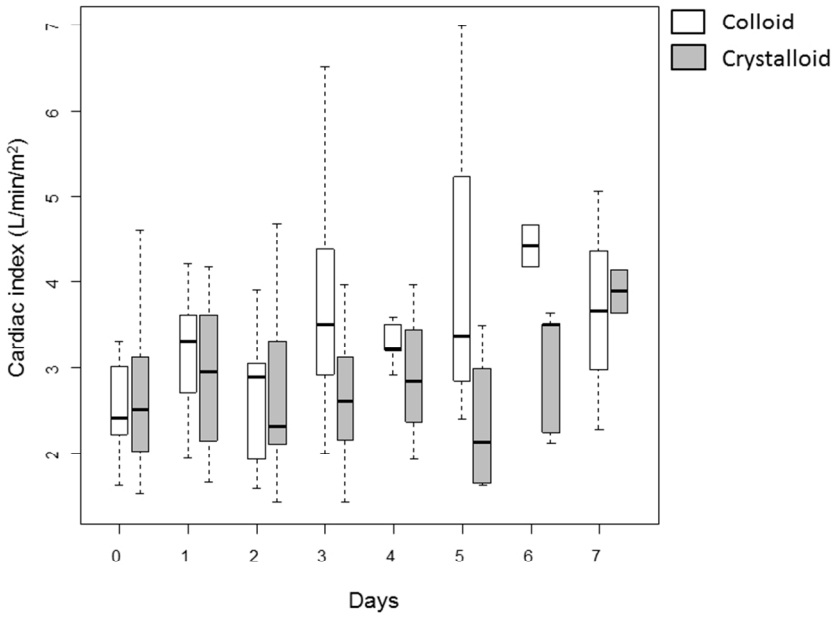

Figure 2

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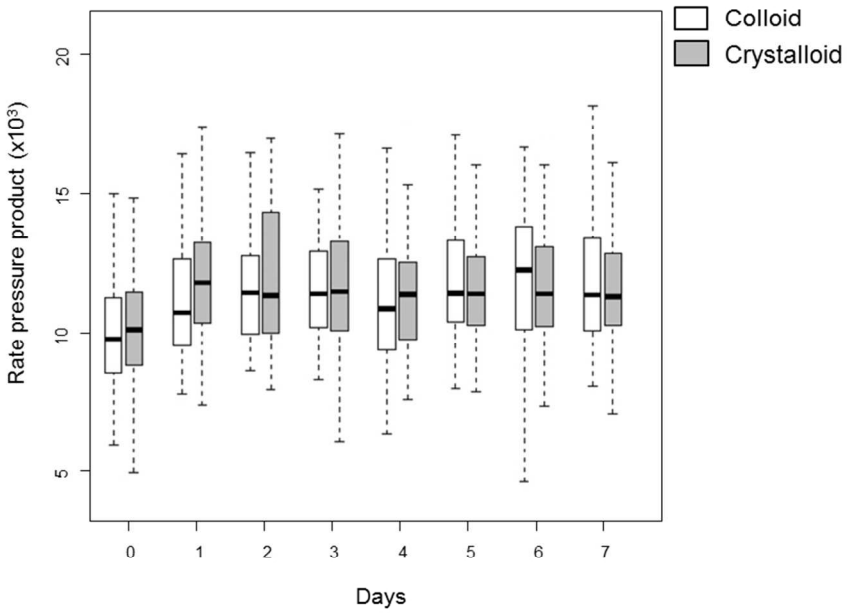

Figure 3

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SUPPLEMENTAL DATA

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

Heming, Nicholas MD[1]; Elatrous, Souheil MD[2]; Jaber, Samir MD, PhD[3]; Dumenil, Anne Sylvie MD[4]; Cousson, Joël MD[5]; Forceville, Xavier MD[6]; Kimmoun, Antoine MD[7]; Trouillet, Jean Louis MD[8]; Fichet, Jérôme MD[9]; Anguel, Nadia MD[10]; Darmon, Michael MD[11]; Martin, Claude MD, PhD[12]; Chevret, Sylvie MD, PhD[13]; Annane, Djillali MD, PhD[1]; for the CRISTAL Investigators

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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)

Supplemental Figures

Supplemental Figure 1: Box-plot showing systolic blood pressure distribution over the first seven days following randomisation in both arms.

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

Supplemental Figure 2: Box-plot showing diastolic blood pressure distribution over the first seven days following randomisation in both arms.

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

Supplemental Figure 3: Box-plot showing mean blood pressure distribution over the first seven days following randomisation in both arms.

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

Supplemental Figure 4: Box-plot showing central venous pressure distribution over the first seven days following randomisation in both arms.

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

Supplemental Figure 5: Box-plot showing pH distribution over the first seven days following randomisation in both arms.

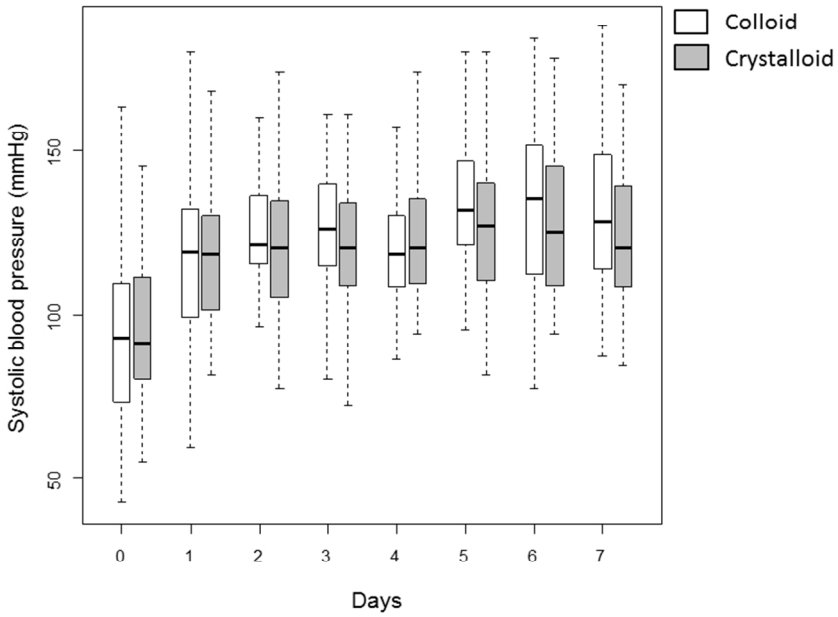
The horizontal line in the box indicates the median value while the lines at the top and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.

Supplemental Figure 6: Box-plot showing blood bicarbonate distribution over the first seven days following randomisation in both arms.

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

Supplemental Figure 7: Box-plot showing arterial lactate distribution over the first seven days following randomisation in both arms.

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



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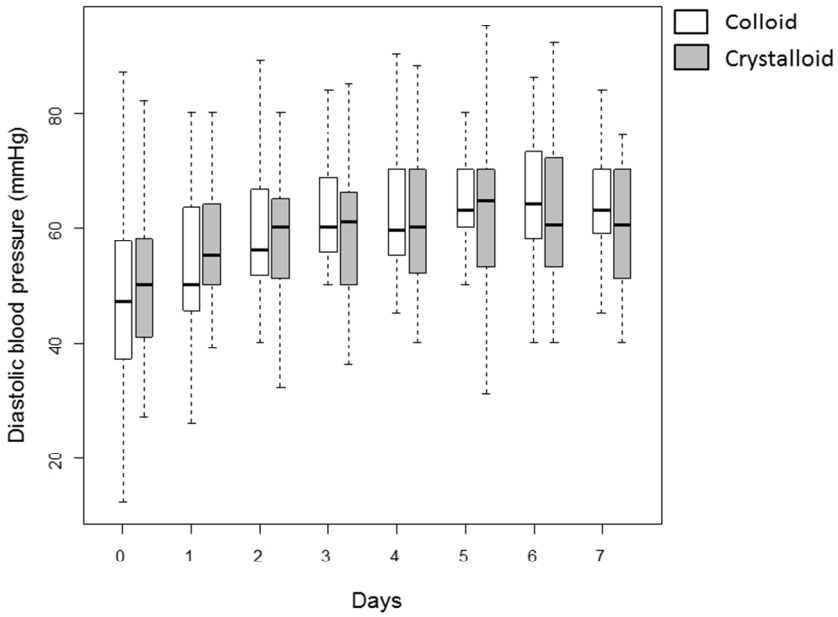

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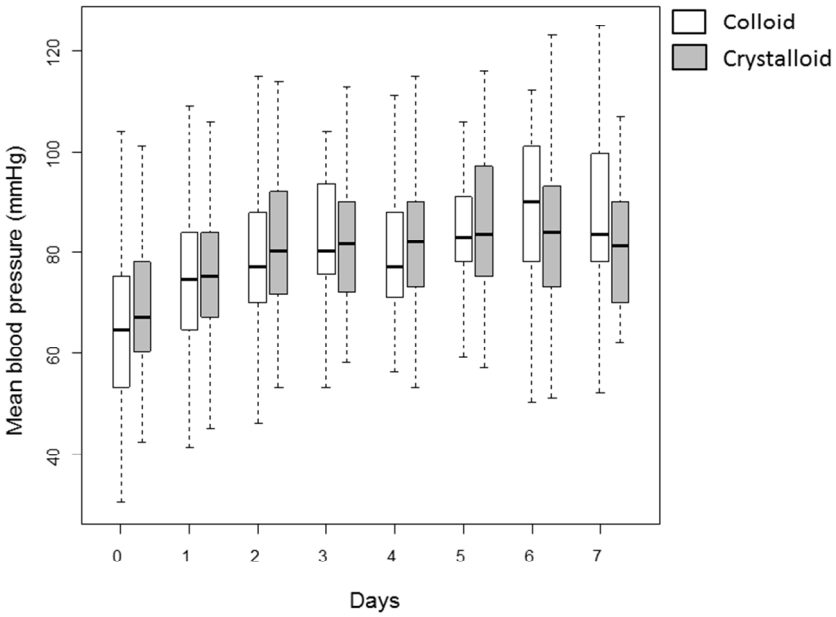

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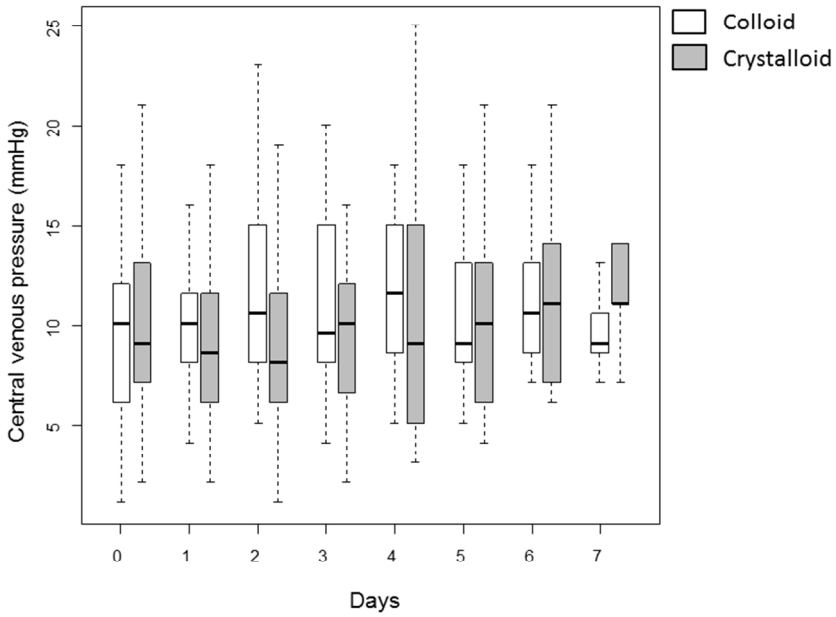

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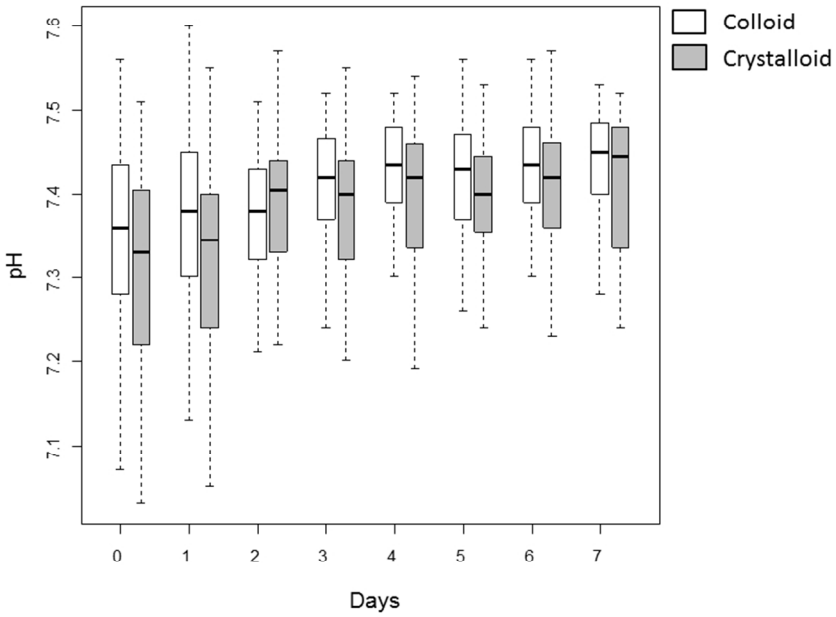

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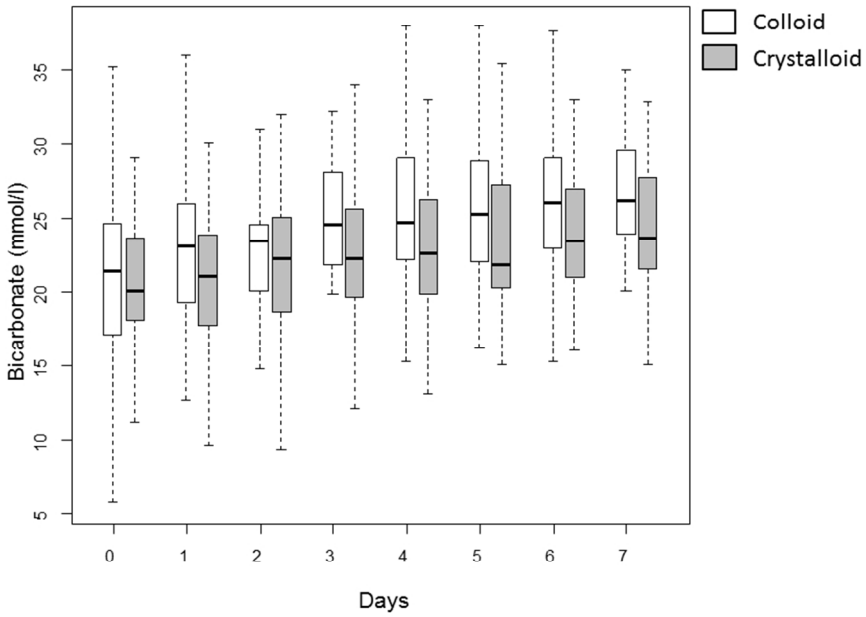

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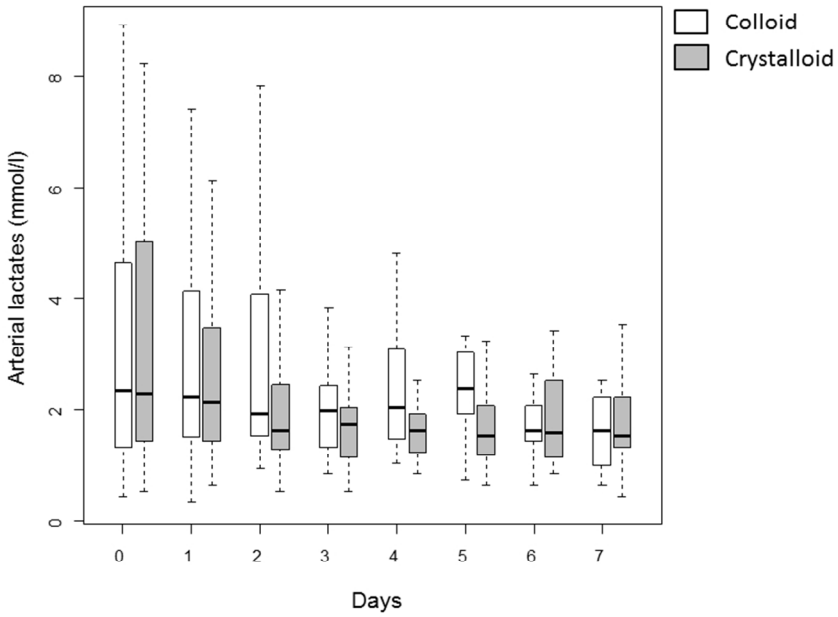

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

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.

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Fluid resuscitation, Intensive Care Unit (ICU), Pulmonary artery catheter, Crystalloid, Colloid

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

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Keywords: Fluid resuscitation; Crystalloid; Colloid; Pulmonary artery catheter; Intensive Care Unit (ICU).

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Abstract

Objective: To compare the hemodynamic effect of crystalloids and colloids during acute severe hypovolemic shock.

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

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

Participants: 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.

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

Outcome measures: 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.

Conclusions: During acute severe hypovolemic shock, patients monitored by a pulmonary artery catheter achieved broadly similar hemodynamic outcomes, using lower volumes of colloids than crystalloids. The heart rate was lower in the colloids arm.

Strengths of the study include:

- Large international multicenter trial, comparing the hemodynamic effect of crystalloids vs. colloids in severe hypovolemic shock. The subgroup analysis met recognized criteria of robustness.
- The CRISTAL trial was a pragmatic, open label trial.

Limitations of the study include:

- Pulmonary artery catheter monitoring was left at the patient's physician discretion resulting in missing data.
- Results should be considered exploratory.

Introduction

Fluid resuscitation is a cornerstone of the management of hypovolemia. [1] During hypovolemic shock, fluids restore intravascular volume, cardiac output, oxygen delivery and reverse peripheral hypoperfusion. [2] Resuscitation fluids are divided into two distinct categories, crystalloids and colloids. [3] 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. [4 5 6] On the other hand, colloids are composed of large molecules, increasing their vascular retention and are theoretically more effective for fluid resuscitation. [7 8] 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. [9-11] A series of large clinical trials were recently undertaken aiming at determining which fluid was superior for the resuscitation of critically ill patients. [12-16] The Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial addressed the issue using a pragmatic approach; rather than studying one fluid versus another, both categories of fluids, crystalloids and colloids were compared in severe hypovolemia. [17] The CRISTAL trial included 2857 subjects treated in 57 intensive care units (ICU). The primary outcome, 28 day mortality, did not significantly differ, with 25.4% mortality in the colloids arm vs. 27% in the crystalloids arm. This finding was similar to results from previous large trials comparing a single colloid to a single crystalloid. [13-15] However, mortality by 90 days was significantly lower in the colloids arm than in the crystalloids arm (30.7% vs. 34.2%). This finding was deemed exploratory. Additionally, the number of days alive at 7 and 28 days

without vasopressor therapy was higher in the colloids than in the crystalloids arm. We sought to compare the effect of crystalloids to that of colloids on hemodynamic parameters during hypovolemic shock. The pulmonary artery catheter (PAC) provides a reliable and reproducible measure of cardiac output as well as the pulmonary artery pressure, pulmonary artery occlusion pressure and derived variables. [18] Therefore, the current study aimed at assessing the hemodynamic effect of crystalloids vs. colloids in the CRISTAL participants monitored by pulmonary artery catheter.

Materials and Methods

1) Study setting and patients

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

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.

2) 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 [19] and disability scale score. [20]

Severity scores including the Glasgow coma score, [21] Simplified Acute Physiology Score II (SAPS II) [22] and the Sequential Organ Failure Assessment (SOFA) Score. [23] 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 (Table S1).

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 SvO_2. 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. [24]

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 and the administration of vasopressors.

3) Statistical analysis

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 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. 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) ≥ 65 mm Hg, urine output ≥ 0.5 mL/kg/h, CVP between 8 and 12 mmHg and SvO_2 ≥ 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 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.

Results

Patients

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. PAC was generally in place around the time of randomization, either before (n = 79; 36%) or within 24 hours post randomization (n = 84; 38%). Characteristics of the subgroup of PAC-monitored patients were similar to those of the whole population of the CRISTAL study, regarding age, gender and initial severity scores (Table 1). Hemodynamic variables at the time of randomisation are described in Table 2.

Treatment effects on hemodynamic variables

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)). The distribution of fluid types within each study arm is displayed in the supplementary files (Table S2). 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) (Figures S1, S2 and S3). 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) (Figure S4). 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) (Figures S5, S6 and S7). Mixed venous oxygen saturation, daily urine output (Figure S8), 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 and a similar use of blood transfusion (Table 3). Other relevant outcomes did not significantly differ between both groups. No serious adverse advent related to PAC placement was reported during the trial.

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.

Sepsis subgroup

Among PAC-monitored patients, 108 subjects were stratified in the sepsis group, of which 52 were allocated to colloids and 56 to crystalloids. We compared the number of patients achieving mean blood pressure levels ≥ 65 mm Hg and urine output ≥ 0.5 mL/kg/h within the first 6 hours. [24] A total of 35/51 (69 %) patients in the crystalloids arm achieved MAP ≥ 65 mm Hg after 6 hours vs. 31/47 (66%) in the colloids arm (*P* = .8); 25/38 (66%) patients in the crystalloids arm achieved urine output ≥ 0.5 mL/kg/h after 6 hours vs. 17/28 (61%) in the colloids arm (*P* = .8). Limited data

precluded the analysis of CVP and SvO_2 values during the first six hours following randomisation.

Discussion

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. [24] The fact that the mean arterial blood pressure and cardiac index did not significantly differ in both groups may be explained by the fact that physicians sought to achieve similar targets in both groups, whether by the administration of fluids, packed blood or vasopressors.

Tachycardia may increase myocardial work, with subsequent excessive myocardial energy expenditure, [27] and may be associated with worse outcomes through excessive cardiovascular morbi-mortality. [28 29] Myocardial protection is of particular interest in the aging population currently common in most ICUs, since it may somewhat relieve cardiovascular mortality.

The efficacy of fluid resuscitation is determined by the capacity of administered fluids to remain in the intravascular space. [1] The superior oncotic pressure of colloids is associated with increased intravascular expansion capacity compared to crystalloids. In order to achieve similar resuscitation goals, compared to colloids, between 20 and 50% more volume of crystalloids should be administered. [12 13 17 30] Inflammatory states such as those observed during critical illness are usually associated with endothelial dysfunction, leading to interstitial oedema. Reducing volumes of administered fluids may be of clinical benefit and a negative fluid balance improved outcome in ARDS, a frequent complication of sepsis. [31 32] In septic shock, a positive

fluid balance has been associated with a worse outcome. [33] However, short term hemodynamic benefits of fluids may in some cases be offset by long term deleterious consequences. Indeed, some types of colloids may be unsafe. Starches, the most commonly used colloid, may be associated with increased risk of acute kidney injury and increased need for renal replacement therapy, both in the general ICU population and in sepsis. [12 13 16] The daily total volume of hydroxyethyl starch which could not exceed 30ml/kg in the CRISTAL trial, lead patients having exceeded that limit to subsequently receive crystalloids. The use of starches has now been restricted in the ICU in Europe and the US. [34 35] 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.

Our findings are similar to those of several of the other major fluid trials. Most trials compared one type of colloid to one type of crystalloid. The SAFE study assessed 4% albumin or 9‰ saline in critically ill patients. [14] Albumin administration was associated with a statistically significant lower heart rate on the first day of treatment, although the difference was small. The ALBIOS study compared 20% albumin (titrated to achieve a serum albumin concentration of over 30 g/L) to 9‰ saline in patients suffering from severe sepsis. [15] Over the first 7 days after randomization, patients in the albumin arm experienced lower heart rate and a shorter duration of vasopressor therapy. The CHEST trial randomized critically ill patients to receive hydroxyethyl starches or 9‰ saline. [13] Among the various hemodynamic targets, higher central venous pressure over the first four days following randomization was the only statistically significant difference between hydroxyethyl starches and 9‰

saline treated patients. The authors of the CHEST study concluded that crystalloids were as effective as colloids for initial resuscitation. The Scandinavian 6S trial allocated either hydroxyethyl starches or Ringer's acetate to severe sepsis patients. [12] The hemodynamic targets were similar between both arms over the first 24 hours after randomization. Of note, subjects enrolled in both CHEST and 6S studies were enrolled up to 24 hours after their admission to the ICU, hence after the initial resuscitation phase. However, in CRISTAL, patients were randomized and treated as early as possible after the occurrence of shock. Patients in CRISTAL were treated by a variety of colloids including starches, but also gelatins, in approximately a third of patients. Gelatins have been less extensively studied in large clinical trials and their drawbacks are not as well characterised. Their use may have somewhat offset any deleterious effect related to starches when administered in the colloid group. Overall these findings should help expand our knowledge pertaining to the field of fluid resuscitation.

Our study has some 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.

Conclusion: CRISTAL participants monitored by a pulmonary artery catheter reached broadly similar hemodynamic outcomes whether treated by crystalloids or by colloids. Colloids were associated with lower heart rates and lower volume of administered fluids than crystalloids.

Authors' Contributions: NH, SC, DA were involved in study concept and design; NH, SE, SJ, A-SD, JC, XF, AK, J-LT, JF, NA, MD, CM acquired the data; SC was involved in the statistical analysis; NH, SC, DA were involved in analysis and interpretation of data; NH and DA drafted the manuscript; all authors critically revised the manuscript for important intellectual content; DA was involved in study supervision. All authors read and approved the final manuscript.

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Competing interests: None declared.

Data sharing statement: Individual data are available by contacting DA at djillali.annane@aphp.fr

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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

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

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

Table 2. Physiological values at baseline according to randomisation

	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/m² (n = 38)	20 [14 ;31]	20 [14 ;33]	17 [14 ;29]	0.73
Right ventricular stroke work index, median [IQR], g.m/m² (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

SvO_2: mixed venous oxygen saturation

Table 3. Study outcome and blood transfusion by treatment group

	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

Figure Legend

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

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

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

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

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

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

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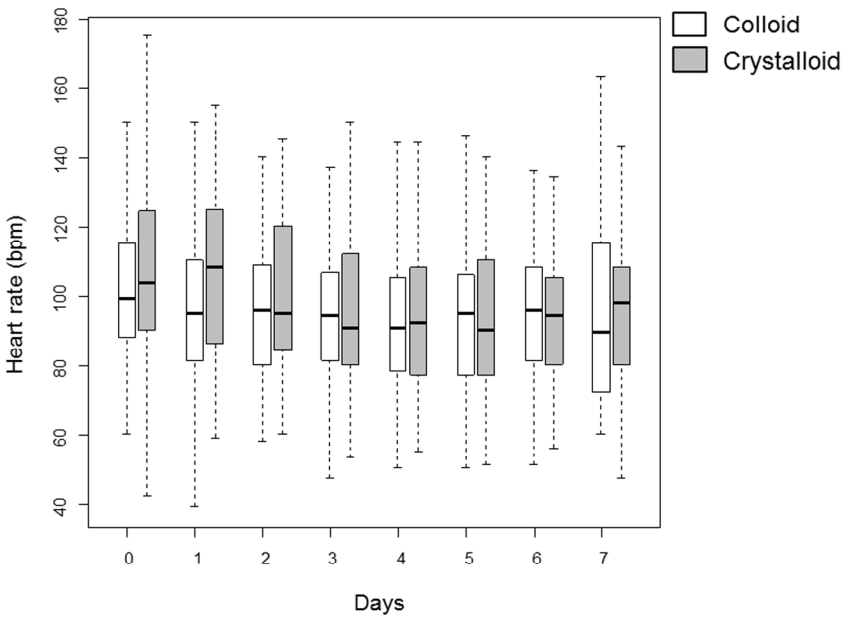

Figure1

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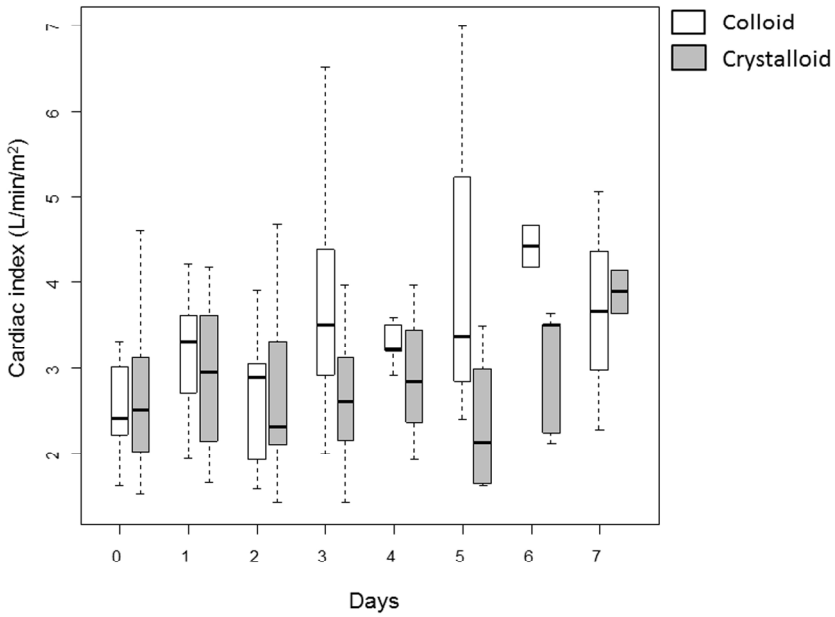

Figure2

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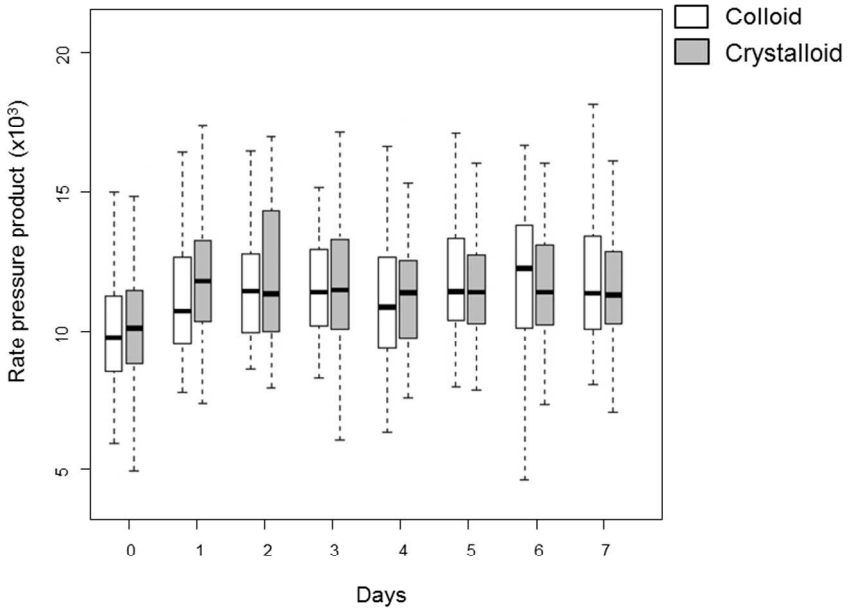

Figure3

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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)

Supplemental Figures

Figure S1: Box-plot showing systolic blood pressure distribution over the first seven days following randomisation in both arms.

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

Figure S2: Box-plot showing diastolic blood pressure distribution over the first seven days following randomisation in both arms.

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

Figure S3: Box-plot showing mean blood pressure distribution over the first seven days following randomisation in both arms.

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

Figure S4: Box-plot showing central venous pressure distribution over the first seven days following randomisation in both arms.

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

Figure S5: Box-plot showing pH distribution over the first seven days following randomisation in both arms.

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

Figure S6: Box-plot showing blood bicarbonate distribution over the first seven days following randomisation in both arms.

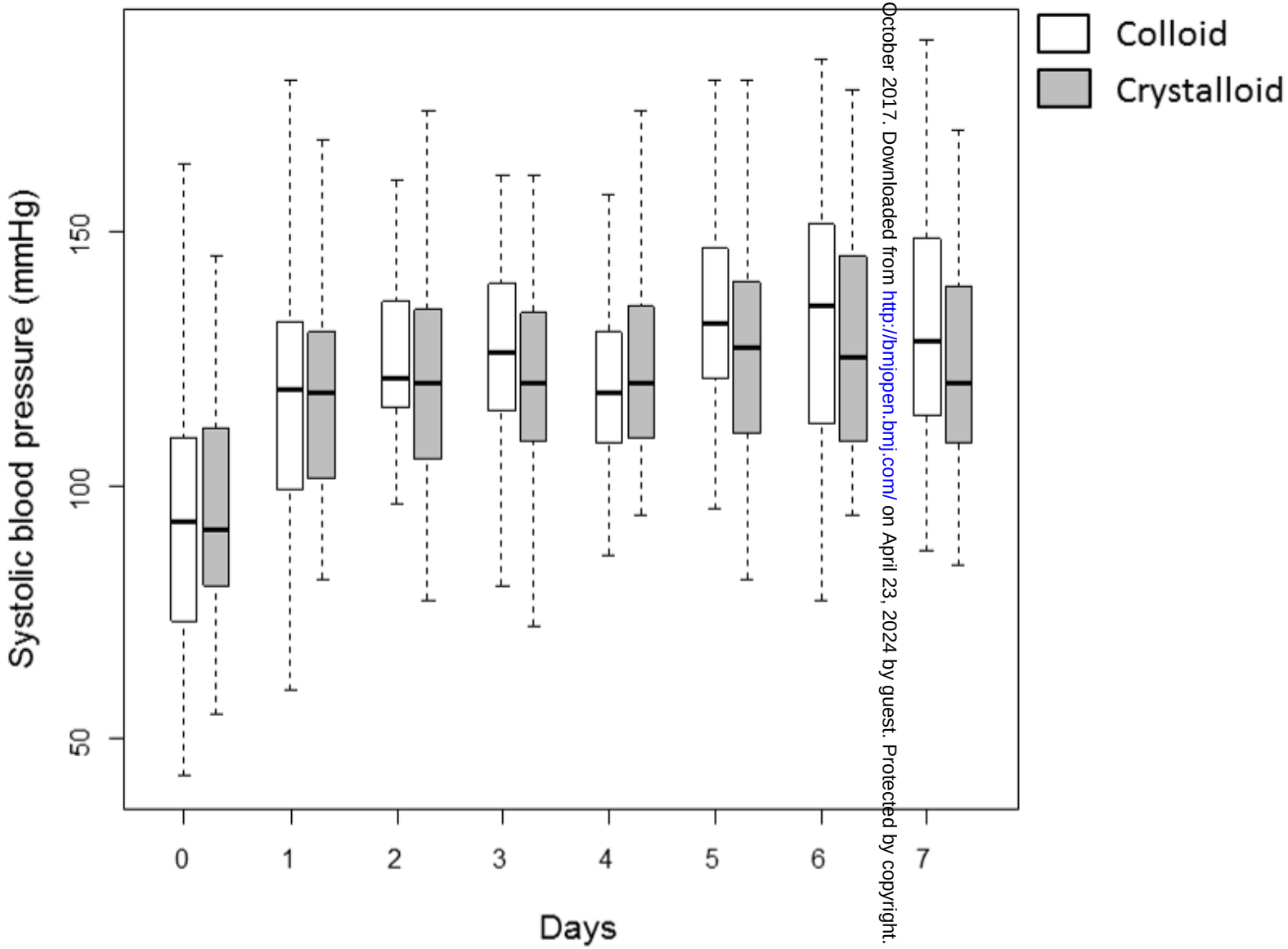
The horizontal line in the box indicates the median value while the lines at the top and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.

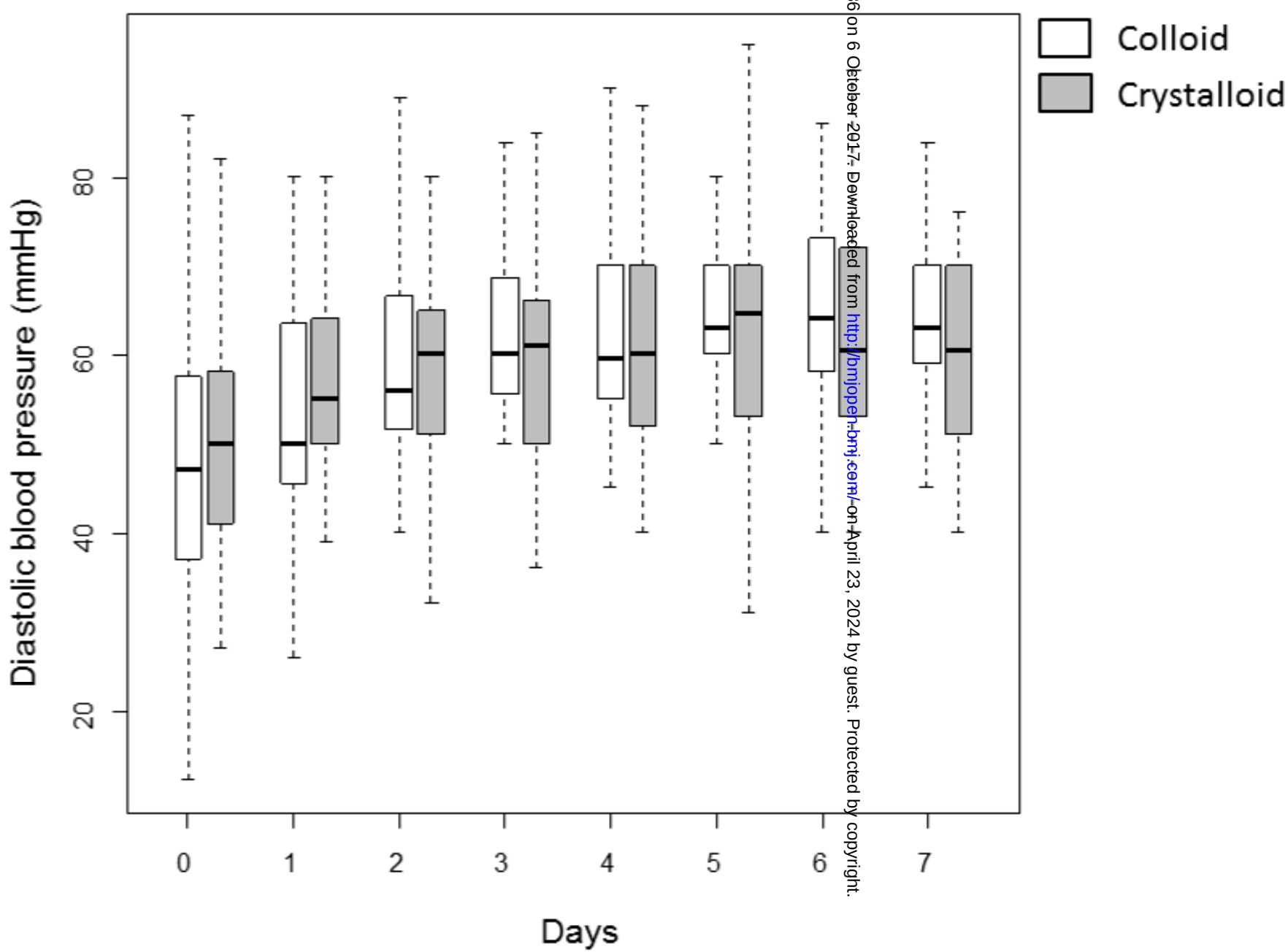
Figure S7: Box-plot showing arterial lactate distribution over the first seven days following randomisation in both arms.

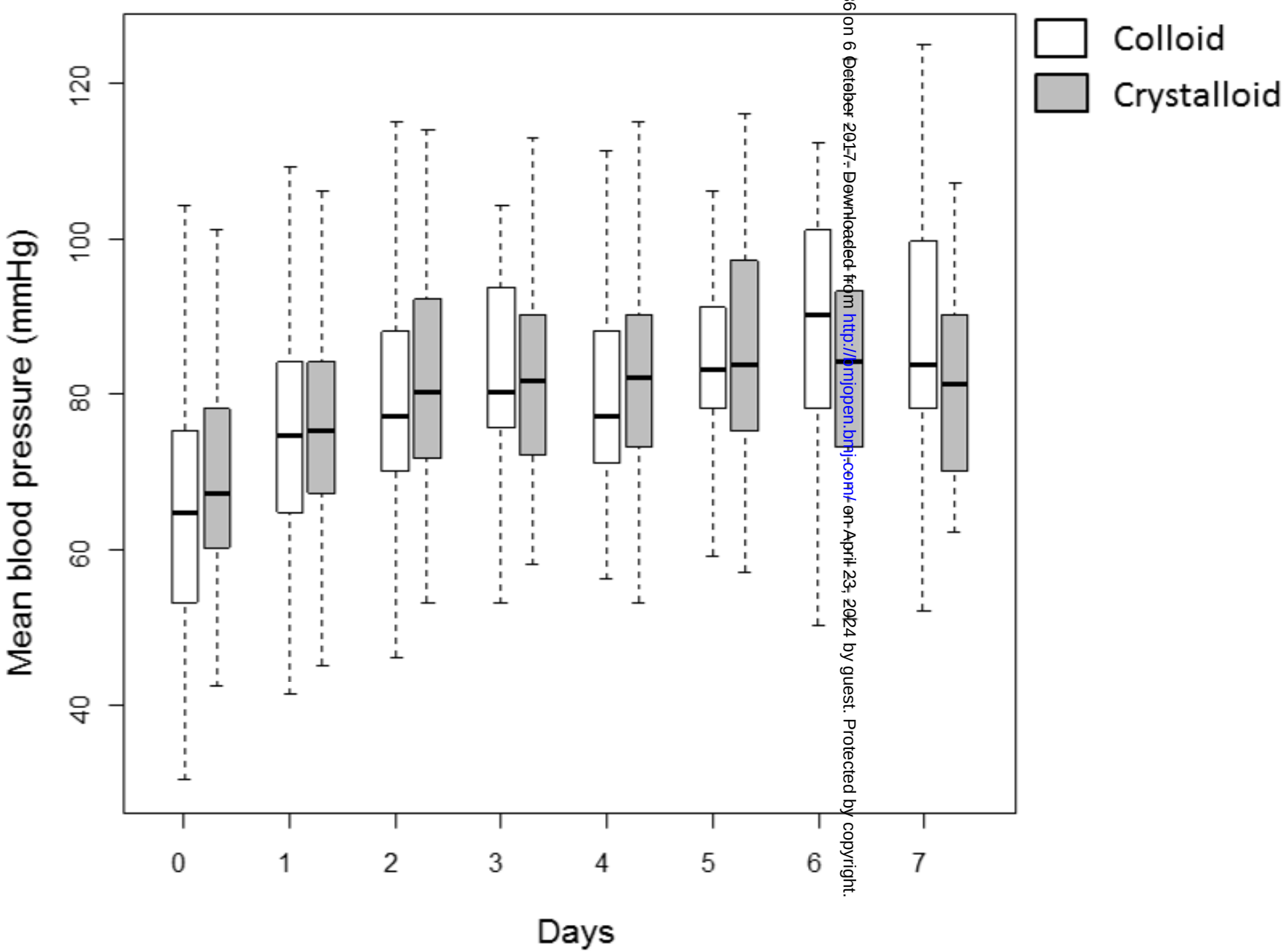
The horizontal line in the box indicates the median value while the lines at the top and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.

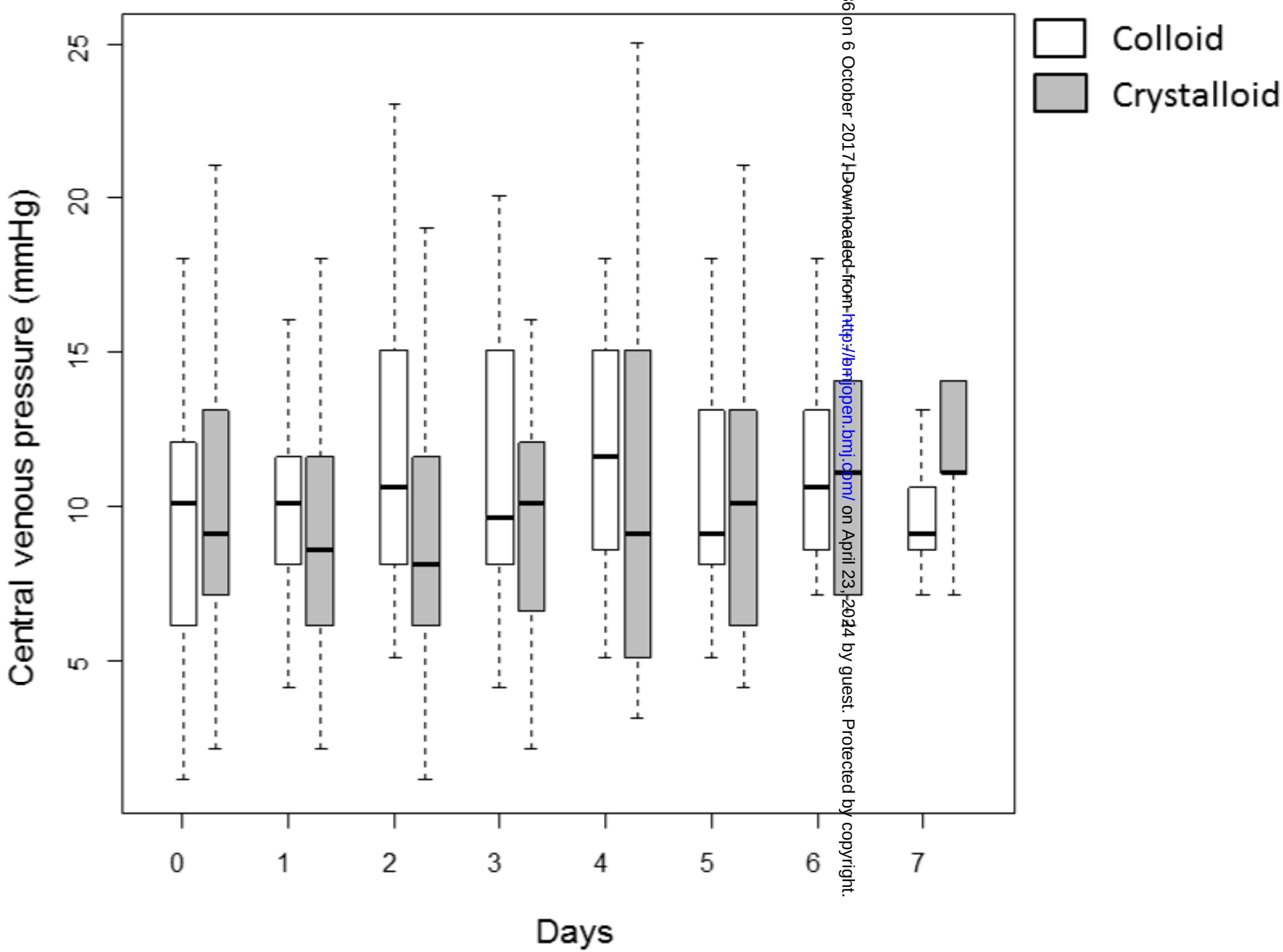
Figure S8: Box-plot showing daily urine output over the first seven days following randomisation in both arms.

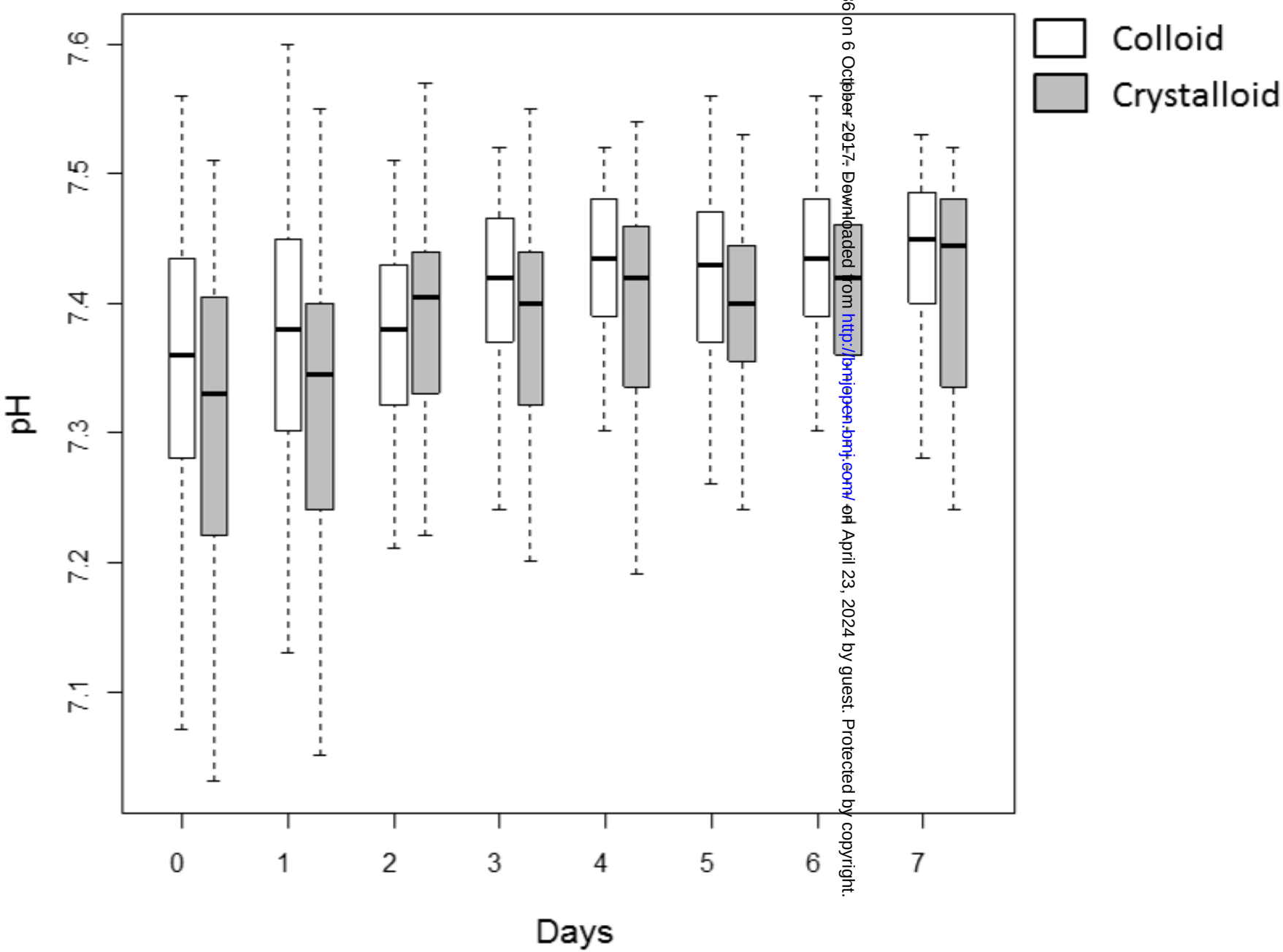
The horizontal line in the box indicates the median value while the lines at the top and bottom of the box indicate the interquartile range. Day 0 = day of randomisation.

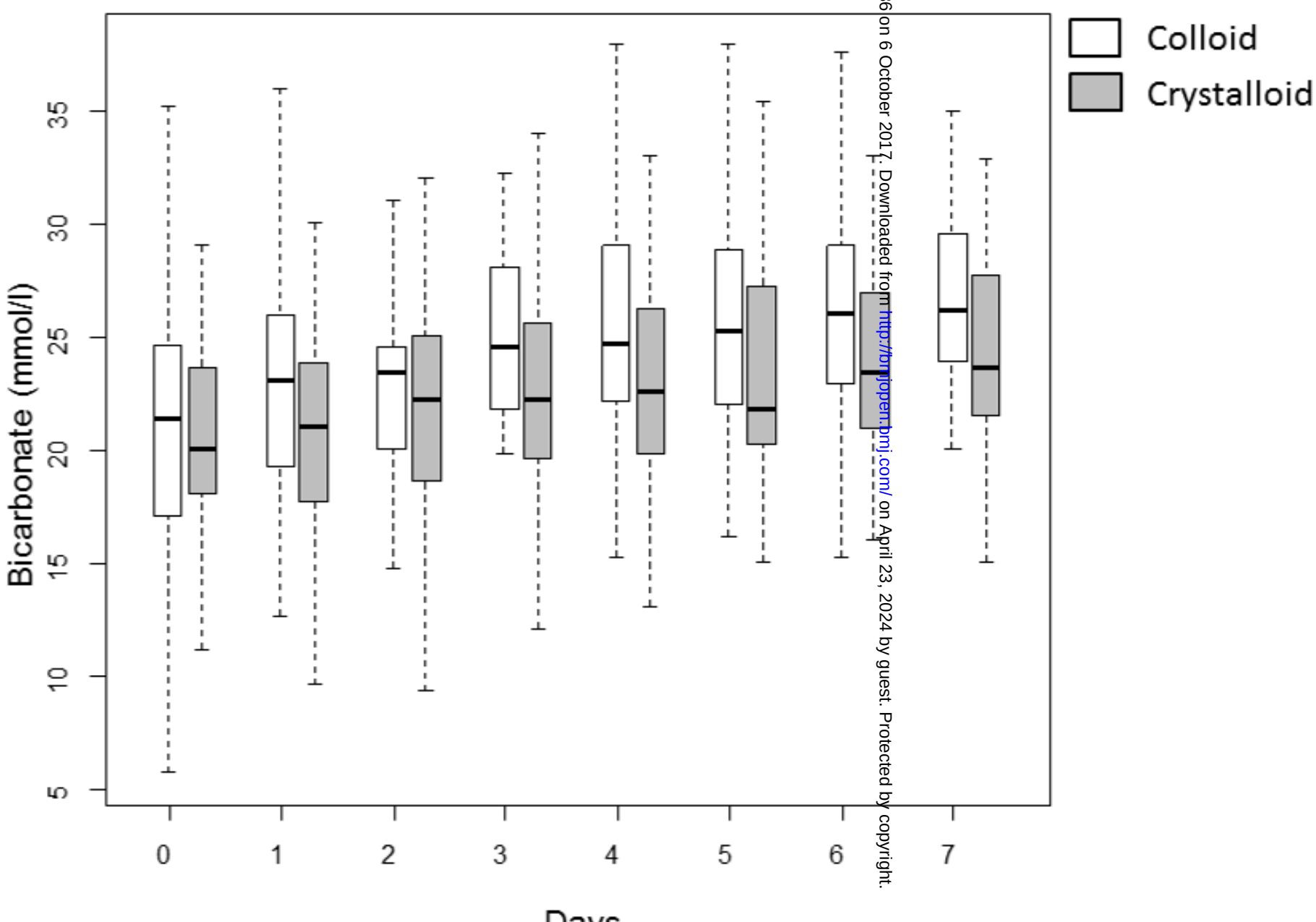


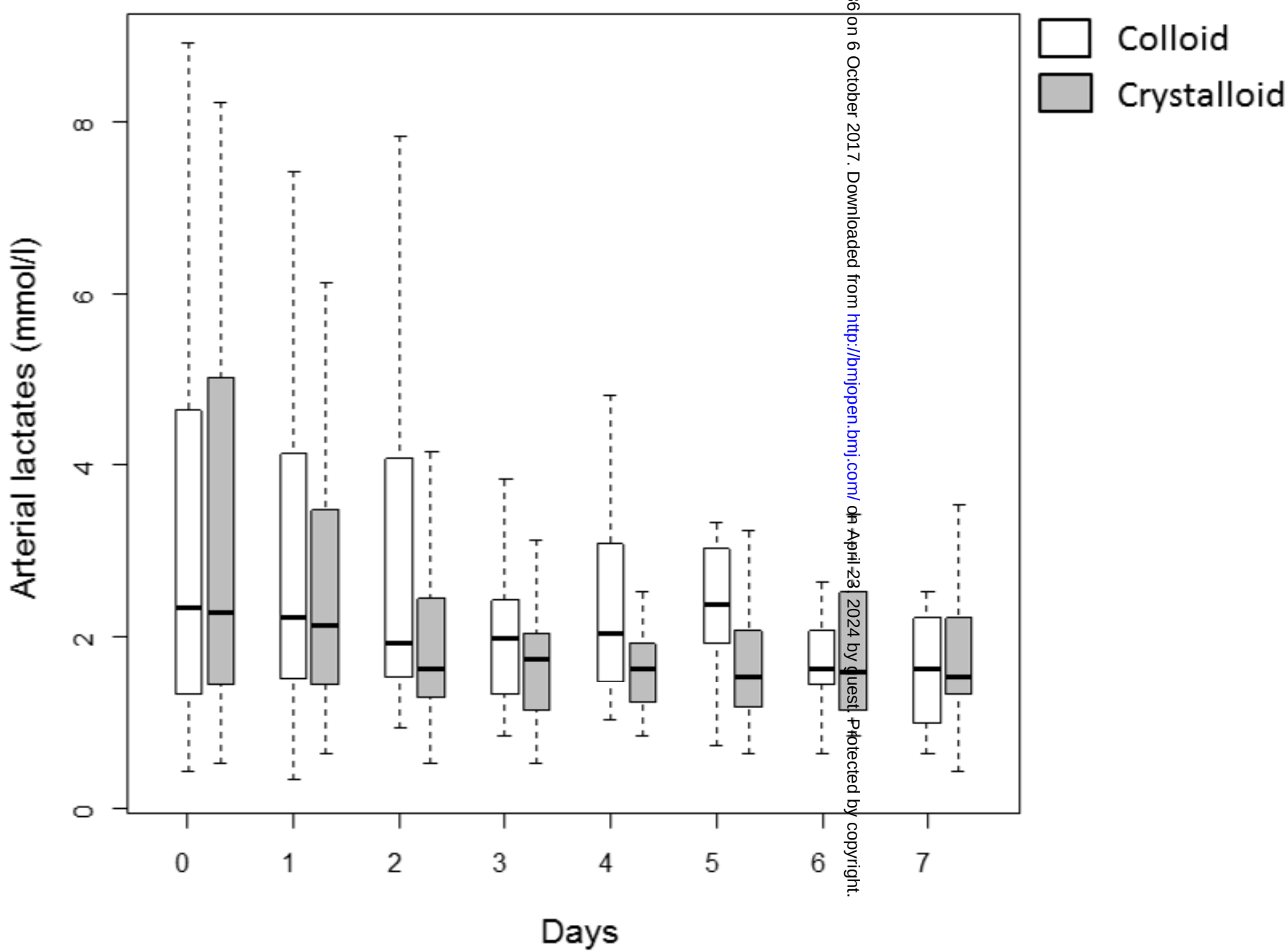


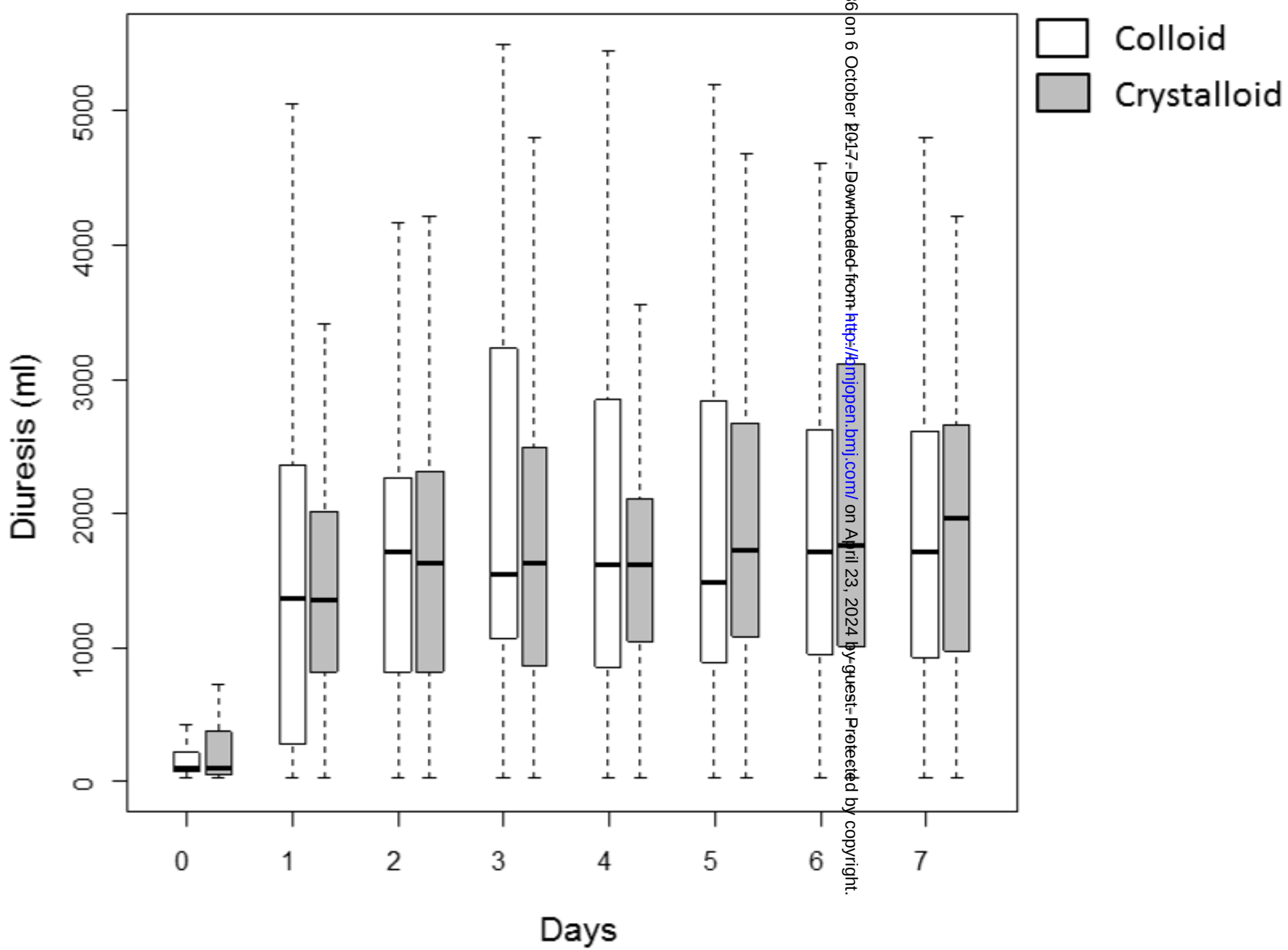












STROBE Statement—checklist of items that should be included in reports of observational studies

	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.

				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 periods of recruitment, exposure, follow-up, and data collection	6-8	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 SvO_2. 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	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	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.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8	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 SvO_2. 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

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).

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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 SvO_2. 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.

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8	Quantitative variables are expressed as median [interquartile range] 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) ≥ 65 mm Hg, urine output ≥ 0.5 mL/kg/h, CVP between 8 and 12 mmHg and SvO_2 ≥ 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.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8	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

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) ≥ 65 mm Hg, urine output ≥ 0.5 mL/kg/h, CVP between 8 and 12 mmHg and SvO_2 ≥ 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

				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 *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	8	Complete cases analysis was undertaken.
		(*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.

		(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) *Cohort study*—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*	*Cohort study*—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

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 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 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.
	(*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

Continued on next page

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.

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.