ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults

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ABSTRACT

BACKGROUND

Both balanced crystalloids and saline are used for intravenous fluid administration in critically ill adults, but it is not known which results in better clinical outcomes.

METHODS

In a pragmatic, cluster-randomized, multiple-crossover trial conducted in five intensive care units at an academic center, we assigned 15,802 adults to receive saline (0.9% sodium chloride) or balanced crystalloids (lactated Ringer's solution or Plasma-Lyte A) according to the randomization of the unit to which they were admitted. The primary outcome was a major adverse kidney event within 30 days — a composite of death from any cause, new renal-replacement therapy, or persistent renal dysfunction (defined as an elevation of the creatinine level to ≥200% of baseline) — all censored at hospital discharge or 30 days, whichever occurred first.

RESULTS

Among the 7942 patients in the balanced-crystalloids group, 1139 (14.3%) had a major adverse kidney event, as compared with 1211 of 7860 patients (15.4%) in the saline group (marginal odds ratio, 0.91; 95% confidence interval [CI], 0.84 to 0.99; conditional odds ratio, 0.90; 95% CI, 0.82 to 0.99; P=0.04). In-hospital mortality at 30 days was 10.3% in the balanced-crystalloids group and 11.1% in the saline group (P=0.06). The incidence of new renal-replacement therapy was 2.5% and 2.9%, respectively (P=0.08), and the incidence of persistent renal dysfunction was 6.4% and 6.6%, respectively (P=0.60).

CONCLUSIONS

Among critically ill adults, the use of balanced crystalloids for intravenous fluid administration resulted in a lower rate of the composite outcome of death from any cause, new renal-replacement therapy, or persistent renal dysfunction than the use of saline. (Funded by the Vanderbilt Institute for Clinical and Translational Research and others; SMART-MED and SMART-SURG ClinicalTrials.gov numbers, NCT02444988 and NCT02547779.)

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Intravenous crystalloid solutions are commonly administered in critical care, yet the question of whether crystalloid composition affects patient outcomes remains unanswered.[1] Historically, 0.9% sodium chloride (saline) has been the most commonly administered intravenous fluid.[2,3] Data suggest that intravenous saline may be associated with hyperchloremic metabolic acidosis,[4] acute kidney injury,[5] and death.[6,7] Crystalloid solutions with electrolyte compositions closer to that of plasma (balanced crystalloids, such as lactated Ringer's solution or Plasma-Lyte A) represent an increasingly used alternative to saline.[8] Several observational studies[6,9,10] and a before-and-after trial[5] suggested that the use of balanced crystalloids is associated with lower rates of acute kidney injury, renal-replacement therapy, and death. However, in two pilot trials,[11,12] no significant difference in any patient outcome was reported between those who received balanced crystalloids and those who received saline.

To determine the effect of isotonic crystalloid composition on clinical outcomes in critically ill adults, we conducted the Isotonic Solutions and Major Adverse Renal Events Trial (SMART), which compared the use of balanced crystalloids with the use of saline in patients in medical (SMART-MED) and nonmedical (SMART-SURG) intensive care units (ICUs). We hypothesized that the use of balanced crystalloids would result in a lower overall incidence of death, new renal-replacement therapy, and persistent renal dysfunction than saline.

Methods

Trial Design and Oversight

We conducted a pragmatic, unblinded, cluster-randomized, multiple-crossover trial in which the use of balanced crystalloids was compared with saline for intravenous fluid administration among critically ill adults admitted to five ICUs at Vanderbilt University Medical Center between June 1, 2015, and April 30, 2017. The trial was approved by the institutional review board at Vanderbilt University with a waiver of informed consent (see the Supplementary Appendix, available with the full text of this article at NEJM.org), was registered online before initiation, and was overseen by an independent data and safety monitoring board. The protocol, available at NEJM.org, and the statistical analysis plan were published before the conclusion of enrollment.[13] All authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Trial Sites and Patient Population

All adults (18 years of age or older) who were admitted to a participating ICU during the trial period were enrolled at the time of ICU admission (site characteristics are described in the Supplementary Appendix). Enrolled patients who were discharged from the hospital were eligible to participate again if they were readmitted to a participating ICU. We assessed the effect of repeat hospitalizations in individual patients in sensitivity analyses. Patients who were admitted to a non-ICU ward from the emergency department were enrolled in a separate trial (Saline against Lactated Ringer's or Plasma-Lyte in the Emergency Department [SALT-ED]) in which balanced crystalloids and saline were compared among adults who were not critically ill. The results of that trial are also reported in this issue of the *Journal*.[14]

Randomization

For each month of the trial, participating ICUs were assigned to use either balanced crystalloids or saline for any intravenous administration of isotonic crystalloid. ICUs were randomly assigned to use saline during even-numbered months and balanced crystalloids during odd-numbered months, or vice versa (Fig. S1 in the Supplementary Appendix). To allow coordination of crystalloid use between ICUs and the emergency department and operating rooms, the three ICUs that admit the majority of patients from the emergency department underwent randomization together, as did the two ICUs that admit the majority of patients from operating rooms.[13] Patients, clinicians, and investigators were aware of group assignments.

Treatments

Patients in the saline group received 0.9% sodium chloride when intravenous isotonic crystalloid was administered, whereas patients in the balanced-crystalloids group received either lactated Ringer's solution or Plasma-Lyte A, according to the preference of the treating clinician (Table S1 in the Supplementary Appendix). An electronic advisor

within the electronic order-entry system informed providers about the trial, asked about relative contraindications to the assigned crystalloid, and, if none were present, guided providers to order the assigned crystalloid. Relative contraindications to the use of balanced crystalloids included hyperkalemia and brain injury. The treating clinician determined the severity of hyperkalemia or brain injury at which saline rather than balanced crystalloids would be used. The unassigned crystalloid was also available from the pharmacy when clinicians believed it to be required for the safe treatment of any patient.

The trial was coordinated with the emergency department and operating rooms so that when feasible, patients being admitted to a participating ICU or receiving a surgical intervention during ICU admission would receive the crystalloid assigned to that ICU.[15] The need for access to an intravenous crystalloid at all times precluded the use of washout periods, and patients who remained in the ICU from the end of one calendar month to the start of another may have been exposed to both types of crystalloid. The effect of dual exposure was evaluated in prespecified sensitivity analyses.

DATA COLLECTION

We used data collected in routine care and electronically extracted from electronic health records.[12,16] These data included information on pre-enrollment renal function, demographic characteristics, diagnoses, predicted risk of in-hospital death, orders for intravenous fluids and blood products, plasma electrolyte and creatinine values, receipt of renal-replacement therapy, and vital status at hospital discharge. Trial personnel who were unaware of group assignment performed manual chart reviews to confirm receipt of renal-replacement therapy and identify indications for new renal-replacement therapy.

OUTCOMES

The primary outcome was the proportion of patients who met one or more criteria for a major adverse kidney event within 30 days[16-20] — the composite of death, new receipt of renal-replacement therapy, or persistent renal dysfunction (defined as a final inpatient creatinine value ≥200% of the baseline value) — all censored at hospital discharge or 30 days after enrollment, whichever came first. The National Institute of Diabetes and Digestive and Kidney Diseases work group on clinical trials in acute kidney injury recommends the use of a major adverse kidney event within 30 days as a patient-centered outcome for phase 3 trials.[16,18] We determined a value for baseline creatinine level using a previously described hierarchical approach in which creatinine values obtained during the year before hospitalization were given priority over in-hospital measurements obtained before ICU admission. The baseline creatinine level was estimated with a previously described three-variable formula when no pre-enrollment measurements were available (for details, see the Supplementary Appendix).[16,21] Patients who had received renal-replacement therapy before enrollment were ineligible to meet the criteria for new renal-replacement therapy or persistent renal dysfunction but could qualify for the primary outcome if they died in the hospital.

Secondary clinical outcomes included in-hospital death before ICU discharge or at 30 days or 60 days, as well as ICU-free days, ventilator-free days, vasopressor-free days, and days alive and free of renal-replacement therapy during the 28 days after enrollment.[13] Secondary renal outcomes included new receipt of renal-replacement therapy, persistent renal dysfunction, acute kidney injury of stage 2 or higher as defined in the Kidney Disease: Improving Global Outcomes criteria for creatinine level,[22] the highest creatinine level during the hospital stay, the change from baseline to the highest creatinine level, and the final creatinine level before hospital discharge.[13]

STATISTICAL ANALYSIS

Complete details regarding the sample-size justification have been reported previously.[13] Initially, we planned to enroll 8000 patients during 60 unit-months (12 months in five ICUs) to detect a 12% relative between-group difference[11,12] in the primary outcome of a major adverse kidney event within 30 days, assuming a 22.0% incidence of the outcome in the saline group on the basis of the findings in a previous report.[19] We subsequently obtained observational data for patients admitted to the ICUs involved in the trial in the year before the trial began. These data suggested that the incidence of the outcome in the saline group would be approximately 15.0%. To retain adequate power to detect the

targeted difference in relative risk, in collaboration with the data and safety monitoring board, the duration of the trial was increased to 82 unit-months. Enrolling approximately 14,000 patients during 82 unit-months would provide power of 90% at a type I error rate of 0.05 to detect a relative difference of 12% (an absolute difference of 1.9 percentage points) in the primary outcome between groups.[13] The data and safety monitoring board conducted two interim analyses; details are provided in the Supplementary Appendix.

Analyses were conducted at the level of each patient's hospitalization in an intention-to-treat fashion. Continuous variables are reported as means and standard deviations or as medians and interquartile ranges; categorical variables are reported as frequencies and proportions.

The primary analysis compared the incidence of the primary outcome in the balanced-crystalloids and saline groups with a generalized, linear, mixed-effects model that included fixed effects (group assignment, age, sex, race, source of admission, mechanical-ventilation status, vasopressor receipt, diagnosis of sepsis, and diagnosis of traumatic brain injury) and random effects (ICU to which the patient was admitted) (for details, see the Supplementary Appendix).[23,24] Both conditional (ICU-level) and marginal (population-level) effects are reported.

Prespecified secondary analyses involved a similar approach. First, we compared secondary outcomes between trial groups. Second, we performed subgroup analyses according to type of ICU, source of admission, receipt of mechanical ventilation, receipt of vasopressors, diagnosis of sepsis or traumatic brain injury (for details, see the Supplementary Appendix), baseline renal function, predicted in-hospital mortality, and total volume of isotonic crystalloid administered through day 30. Third, we conducted sensitivity analyses using alternative approaches to addressing the issue of missing data on baseline creatinine level (for details, see the Supplementary Appendix). Fourth, we performed sensitivity analyses according to the volume of crystalloid administered, accounting for crossover and limiting the analyses to each patient's first ICU admission.[13] Other between-group comparisons were made with the Mann–Whitney rank-sum test for continuous variables and the chi-square test for categorical variables.

A two-sided P value of less than 0.048 indicated statistical significance for the primary outcome after accounting for interim analyses. All other analyses were considered to be hypothesis-generating.[13] With 14 secondary outcomes, the likelihood of observing a P value of less than 0.05 for at least one secondary outcome by chance alone was 51.2%. All analyses were performed with the statistical software R, version 3.3.0, with a prespecified analysis code published before the conclusion of enrollment.[13]

RESULTS

BASELINE CHARACTERISTICS

In all, 15,802 patients from five ICUs were enrolled in the trial (Fig. S2 in the Supplementary Appendix). The median age was 58 years, and 57.6% of patients were men. More than one third of patients were receiving mechanical ventilation and one quarter were receiving vasopressors at enrollment. There were no significant differences in baseline characteristics between the patients assigned to receive balanced crystalloids (7942 patients) and those assigned to receive saline (7860 patients) (Table 1, and Tables S2 and S3 in the Supplementary Appendix).

FLUID THERAPY AND ELECTROLYTES

Because the fluid therapy provided in the emergency department and operating room was coordinated with that provided in the ICU to which patients were being admitted, the majority of pre-ICU fluid that patients received was consistent with trial-group assignment (Table S4 in the Supplementary Appendix). The median volume of balanced crystalloids administered to patients in the balanced-crystalloids group between ICU admission and hospital discharge or 30 days (whichever occurred first) was 1000 ml (interquartile range, 0 to 3210), and the median volume of 0.9% sodium chloride administered to patients in the saline group was 1020 ml (interquartile range, 0 to 3500) (Fig. 1, and Tables S5 and S6 in the Supplementary Appendix). Only 426 patients (5.4%) in the balanced-crystalloids group and 343 patients (4.4%) in the saline group received any volume of unassigned crystalloid as a result of remaining in the ICU from one calendar month to the next (Table S5 in the Supplementary Appendix). There was no significant between-group difference in the median

Table 1. Participant Characteristics at Baseline.*

Characteristic	Balanced Crystalloids (N=7942)	Saline (N=7860)
Age — yr		
Median	58	58
Interquartile range	44–69	44–69
Male sex — no. (%)	4540 (57.2)	4557 (58.0)
White race — no. (%)†	6384 (80.4)	6322 (80.4)
Weight — kg‡		
Median	80	79
Interquartile range	69–96	68–95
Coexisting renal conditions — no. (%)		
Chronic kidney disease of stage 3 or higher§	1388 (17.5)	1360 (17.3)
Previous receipt of renal-replacement therapy — no. (%)	384 (4.8)	402 (5.1)
Source of admission to ICU — no. (%)		
Emergency department	3975 (50.1)	3997 (50.9)
Operating room	1732 (21.8)	1649 (21.0)
Transfer from another hospital	1038 (13.1)	1018 (13.0)
Hospital ward	788 (9.9)	780 (9.9)
Outpatient	363 (4.6)	359 (4.6)
Another ICU within hospital	46 (0.6)	57 (0.7)
Diagnosis on ICU admission — no. (%)		
Sepsis or septic shock	1167 (14.7)	1169 (14.9)
Traumatic brain injury	698 (8.8)	665 (8.5)
Mechanical ventilation — no. (%)	2723 (34.3)	2731 (34.7)
Vasopressors — no. (%)	2094 (26.4)	2058 (26.2)
Mean predicted risk of in-hospital death — % (95% CI)¶	9.4 (9.0–9.9)	9.6 (9.2–10.0)
Baseline creatinine level — mg/dl‖		
Median	0.89	0.89
Interquartile range	0.74–1.10	0.74–1.10
Acute kidney injury of stage 2 or higher — no. (%)**	681 (8.6)	643 (8.2)

* There were no significant differences in baseline characteristics between the two study groups (P values range from 0.12 to 0.94). To convert the values for creatinine to micromoles per liter, multiply by 88.4. ICU denotes intensive care unit.

† Race was reported by patients or their surrogates and recorded in the electronic health record as a part of routine clinical care.

‡ Information on weight at enrollment was missing for 698 patients.

§ Chronic kidney disease of stage 3 or higher is defined as a glomerular filtration rate less than 60 ml per minute per 1.73 m^2, as calculated with the equation developed by the Chronic Kidney Disease Epidemiology Collaboration[25] with the patient's baseline creatinine value.

¶ Predicted risk of in-hospital death is an estimated probability of death before hospital discharge generated through the Vizient database (formerly known as the University HealthSystem Consortium).[26] Information on the predicted risk of in-hospital death was missing for 126 patients.

‖ For the purposes of the trial, the baseline creatinine level was defined as the lowest plasma creatinine level measured in the 12 months preceding hospitalization, unless not available, in which case the lowest plasma creatinine level measured between hospitalization and admission to the ICU was used. An estimated creatinine level was used for patients for whom there was no level available from the 12 months before hospitalization to the time of admission to the ICU. Baseline creatinine levels were estimated for a total of 863 patients (10.9%) in the balanced-crystalloids group and 826 patients (10.5%) in the saline group (Table S3 in the Supplementary Appendix).

** Acute kidney injury of stage 2 or higher is defined according to the Kidney Disease: Improving Global Outcomes creatinine criteria[22] as a first plasma creatinine value after enrollment of at least 200% of the baseline value or both a value greater than 4.0 mg per deciliter (350 μmol per liter) and an increase of at least 0.3 mg per deciliter (27 μmol per liter) from the baseline value.

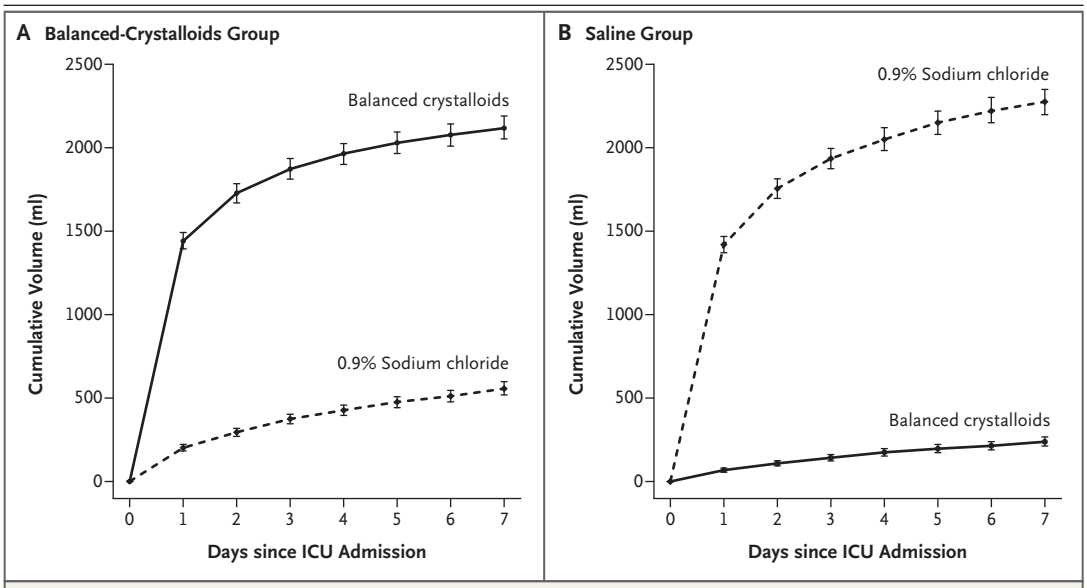


Figure 1. Volume of Intravenous Isotonic Crystalloid Administered According to Group.

The cumulative volume of intravenous balanced crystalloids (solid line) and 0.9% sodium chloride (dotted line) between admission to the intensive care unit (ICU) and hospital discharge is shown for patients in the balanced-crystalloids group (Panel A) and the saline group (Panel B). I bars indicate 95% confidence intervals.

volume of nonisotonic intravenous fluid, blood products, or medications administered (Table S7 in the Supplementary Appendix).

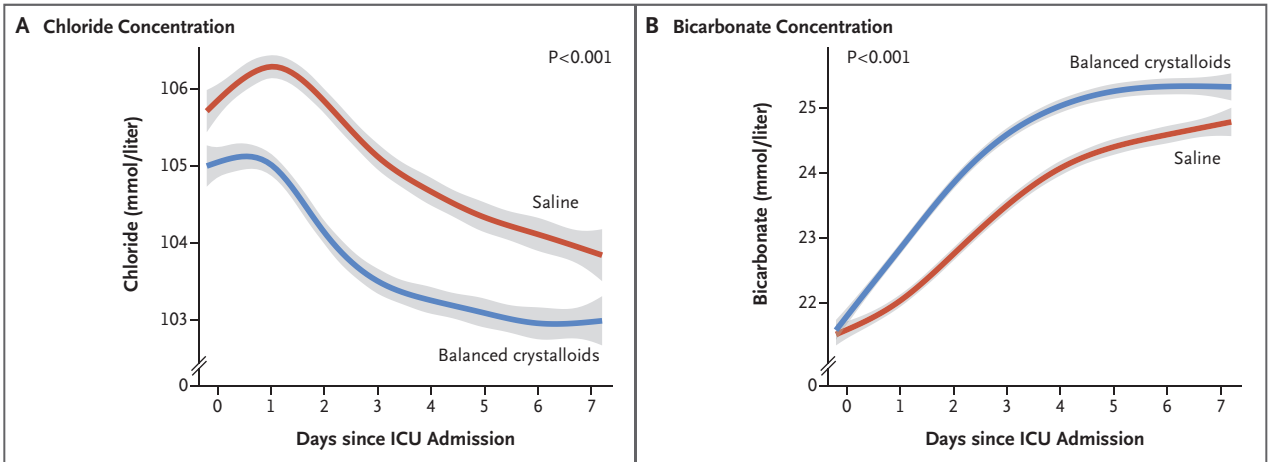
Fewer patients in the balanced-crystalloids group than in the saline group had a measured plasma chloride concentration greater than 110 mmol per liter (24.5% vs. 35.6%, P<0.001) or a plasma bicarbonate concentration less than 20 mmol per liter (35.2% vs. 42.1%, P<0.001) (Fig. 2, and Fig. S3 and Table S8 in the Supplementary Appendix). Differences between groups in chloride and bicarbonate concentration were greater for patients who received larger volumes of isotonic crystalloid (Figs. S4 and S5 in the Supplementary Appendix).

PRIMARY OUTCOME

A total of 1139 patients (14.3%) in the balanced-crystalloids group and 1211 patients (15.4%) in the saline group had a major adverse kidney event (marginal odds ratio, 0.91; 95% confidence interval [CI], 0.84 to 0.99; conditional odds ratio, 0.90; 95% CI, 0.82 to 0.99; P=0.04) (Table 2, and Table S9 and Fig. S6 in the Supplementary Appendix). The results were similar in six prespecified sensitivity analyses: one was restricted to patients who received 500 ml or more of isotonic crystalloid in the 72 hours after enrollment, a second excluded patients admitted in the week preceding a crossover in the fluid assigned to the ICU, a third excluded patients who transferred between ICUs or remained in the ICU through a crossover, a fourth included only the first ICU admission for each patient, a fifth addressed the issue of missing values for baseline creatinine levels, and a sixth used alternative modeling approaches (odds ratios between 0.87 and 0.93 for all sensitivity analyses; see Table S10 in the Supplementary Appendix). In prespecified subgroup analyses, the difference in the rate of the primary outcome between the balanced-crystalloids group and the saline group was greater among patients who received larger volumes of isotonic crystalloid and among patients with sepsis (Fig. 3, and Fig. S7 in the Supplementary Appendix). Among patients with sepsis, 30-day in-hospital mortality was 25.2% with balanced crystalloids and 29.4% with saline (adjusted odds ratio, 0.80; 95% CI, 0.67 to 0.97; P=0.02).

SECONDARY OUTCOMES

A total of 818 patients (10.3%) in the balanced-crystalloids group died before hospital discharge and within 30 days of ICU admission as compared with 875 patients (11.1%) in the saline group (P=0.06) (Table 2, and Figs. S8 and S9 in



No. of Patients with Measurement				
Balanced crystalloids	6904	4715	3263	2195
Saline	6747	4669	3283	2172

No. of Patients with Measurement				
Balanced crystalloids	6929	4718	3266	2198
Saline	6763	4678	3293	2175

Figure 2. Plasma Chloride and Bicarbonate Concentration According to Group.

The mean and 95% confidence interval (denoted by gray shading) for the first measurement of plasma chloride concentration (Panel A) or bicarbonate concentration (Panel B) on the first 7 days since admission to the intensive care unit (ICU) are shown for patients in the balanced-crystalloids group and in the saline group with locally weighted scatterplot smoothing. Plasma chloride and bicarbonate concentrations were similar between groups at presentation (Table S3 in the Supplementary Appendix), but because fluid therapy in the emergency department and operating room was coordinated with the ICU to which patients were being admitted, plasma chloride concentration differed between the balanced-crystalloids and saline groups at the time of ICU admission.

the Supplementary Appendix). A total of 189 patients (2.5%) in the balanced-crystalloids group and 220 patients (2.9%) in the saline group received new renal-replacement therapy (P=0.08) (Table S11 in the Supplementary Appendix). The highest stage of acute kidney injury and the incidence of persistent renal dysfunction did not differ significantly between groups (Table 2, and Table S12 in the Supplementary Appendix).

DISCUSSION

Although both saline and balanced crystalloids have been administered to patients in clinical practice for decades,[3] few trials have addressed the effects of crystalloid composition on clinical outcomes.[1] In preclinical models, the high chloride content of saline has been reported to cause hyperchloremia,[27] acidosis,[27] inflammation,[28] renal vasoconstriction,[29] acute kidney injury,[30] hypotension,[31] and death.[32] Studies involving healthy volunteers suggest saline may decrease renal perfusion through chloride-mediated renal vasoconstriction.[33] Observational studies involving critically ill adults have shown higher rates of acute kidney injury,[34] renal-replacement therapy,[5,10] and death[6,7,9,35] with saline than with balanced crystalloids, although results have been inconsistent.[36] Although underpowered for clinical outcomes, two recent pilot trials involving critically ill adults showed an absolute difference of 1 percentage point in mortality in favor of balanced crystalloids.[11,12]

In the current trial, the use of balanced crystalloids rather than saline resulted in an absolute difference of 1.1 percentage points in favor of balanced crystalloids in the primary outcome. This finding is consistent with the results of the SALT-ED trial conducted concurrently in noncritically ill adults.[14] Although the effect size achieved in the current trial was modest in terms of percentages, if our data on the use of balanced crystalloids were applied to the care of the more than 5 million patients admitted to ICUs each year, the reduction in death, new renal-replacement therapy, or persistent renal dysfunction could be substantial.[37] Our results suggest that the use of balanced crystalloids rather than saline might prevent 1 patient among every 94 patients admitted to an ICU from the need for

Table 2. Clinical Outcomes.*

Outcome	Balanced Crystalloids (N=7942)	Saline (N=7860)	Adjusted Odds Ratio (95% CI)†	P Value†
Primary outcome				
Major adverse kidney event within 30 days — no. (%)‡	1139 (14.3)	1211 (15.4)	0.90 (0.82 to 0.99)	0.04
Components of primary outcome				
In-hospital death before 30 days — no. (%)	818 (10.3)	875 (11.1)	0.90 (0.80 to 1.01)	0.06
Receipt of new renal-replacement therapy — no./total no. (%)§	189/7558 (2.5)	220/7458 (2.9)	0.84 (0.68 to 1.02)	0.08
Among survivors	106/6787 (1.6)	117/6657 (1.8)		
Final creatinine level ≥200% of baseline — no./total no. (%)§	487/7558 (6.4)	494/7458 (6.6)	0.96 (0.84 to 1.11)	0.60
Among survivors	259/6787 (3.8)	273/6657 (4.1)		
Among survivors without new renal-replacement therapy	215/6681 (3.2)	219/6540 (3.3)		
Secondary outcomes				
In-hospital death — no. (%)				
Before ICU discharge	528 (6.6)	572 (7.3)	0.89 (0.78 to 1.02)	0.08
Before 60 days	928 (11.7)	975 (12.4)	0.92 (0.83 to 1.02)	0.13
ICU-free days¶				0.94
Median	25.3	25.3	1.00 (0.89 to 1.13)	
Interquartile range	22.1 to 26.6	22.2 to 26.6		
Mean	21.8±8.3	21.7±8.6		
Ventilator-free days¶			1.06 (0.97 to 1.16)	0.22
Median	28.0	28.0		
Interquartile range	26.0 to 28.0	26.0 to 28.0		
Mean	24.2±8.6	23.9±8.9		
Vasopressor-free days¶			1.05 (0.97 to 1.14)	0.26
Median	28.0	28.0		
Interquartile range	27.0 to 28.0	27.0 to 28.0		
Mean	24.7±8.5	24.4±8.8		
Renal-replacement therapy–free days¶			1.11 (1.02 to 1.20)	0.01
Median	28.0	28.0		
Interquartile range	28.0 to 28.0	28.0 to 28.0		
Mean	25.0±8.6	24.8±8.9		
Secondary renal outcomes§				
Stage 2 or higher AKI developing after enrollment — no./total no. (%)‖	807/7558 (10.7)	858/7458 (11.5)	0.91 (0.82 to 1.01)	0.09
Creatinine — mg/dl**				
Highest before discharge or day 30			1.01 (0.97 to 1.05)	0.58
Median	0.99	0.99		
Interquartile range	0.78 to 1.53	0.78 to 1.52		
Change from baseline to highest value			0.98 (0.94 to 1.02)	0.35
Median	0.04	0.04		
Interquartile range	−0.08 to 0.31	−0.08 to 0.32		

Table 2. (Continued.)

Outcome	Balanced Crystalloids (N=7942)	Saline (N=7860)	Adjusted Odds Ratio (95% CI)†	P Value†
Final value before discharge or 30 days			1.02 (0.97 to 1.06)	0.51
Median	0.83	0.83		
Interquartile range	0.70 to 1.11	0.70 to 1.11		

* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. ICU denotes intensive care unit.

† Categorical outcomes were compared with a generalized, linear, mixed-effects model, with adjustment for the ICU to which the patient was admitted as a random effect and prespecified covariates as fixed effects.[13] Continuous outcomes were compared between groups with a proportional-odds model, with adjustment for the same variables.

‡ A major adverse kidney event within 30 days is the composite of death, receipt of new renal-replacement therapy, or final creatinine level that was at least 200% of the baseline level, with all events censored at hospital discharge or at 30 days after admission to the ICU, whichever occurred first. The effect of study group on major adverse kidney events within 30 days is the conditional effect. The marginal effect yielded an odds ratio of 0.91 and a 95% confidence interval of 0.84 to 0.99.

§ Data on receipt of new renal-replacement therapy, final creatinine level that was at least 200% of the baseline level, and secondary renal outcomes are provided for the 15,016 patients not known to have received renal-replacement therapy before ICU admission.

¶ ICU-free, ventilator-free, vasopressor-free, and renal-replacement-therapy–free days refer to the number of days on which a patient was alive and free from the specified therapy in the first 28 days after enrollment. Odds ratios of higher than 1.0 indicate a better outcome (i.e., more days alive and free from the specified therapy) with balanced crystalloids than with saline.

‖ The development of acute kidney injury (AKI) of stage 2 or higher after enrollment was defined in accordance with the Kidney Disease: Improving Global Outcomes plasma creatinine criteria[22] as any creatinine level between enrollment and discharge or 30 days that increased by at least 0.3 mg per deciliter (27 μmol per liter) from a preceding post-enrollment value and was at least 200% of the baseline value, at least 200% of a preceding post-enrollment value, or at least 4.0 mg per deciliter (350 μmol per liter) or as new receipt of renal-replacement therapy.

** Among patients who had not received previous renal-replacement therapy, the plasma creatinine level was measured a mean of 8.0 times between enrollment and the first of discharge or 30 days in each group; the plasma creatinine level was not measured between enrollment and the first of discharge or 30 days for 418 of 7558 patients (5.5%) in the balanced-crystalloids group and 443 of 7458 patients (5.9%) in the saline group.

new renal-replacement therapy, from persistent renal dysfunction, or from death. Moreover, the difference in outcomes between balanced crystalloids and saline appeared to be greater for patients with sepsis and patients who received larger volumes of isotonic crystalloid.

The appropriate composition of a fluid may depend on the indication for its use and the condition of the individual patient. Concern that the relative hypotonicity of balanced crystalloids could increase intracranial pressure in patients with brain injury led us to systematically present clinicians with the option of administering 0.9% sodium chloride to patients with brain injury, regardless of trial group. Thus, our results cannot be used to provide guidance as to whether balanced crystalloids should be used in patients with traumatic brain injury.

Our trial has several strengths. The large sample size provided statistical power to detect small differences in patient outcomes. As was the case in each of the previous trials that compared balanced crystalloids with saline in critically ill adults,[5,11,12] group assignment in our trial occurred at the level of the ICU. This trial design allowed delivery of the assigned crystalloid early in each patient's critical illness. Enrolling all adults admitted to participating ICUs and allowing clinical providers to deliver the assigned crystalloid during clinical care minimized selection bias and improved generalizability.

The trial also has several limitations. Conduct at a single academic center limits generalizability. Treating clinicians were aware of the composition of the assigned crystalloid and of the group-assignment sequence of their ICU. The outcomes of death and creatinine level are objective, but a clinician's decision to initiate renal-replacement therapy may be susceptible to treatment bias. Censoring data collection at hospital discharge may underestimate the true incidence of death at 30 days and may overestimate the true incidence of persistent renal dysfunction at 30 days.[16] On the basis of the hypothesized mechanism of chloride-induced organ injury or acidosis,[29,33] we evaluated lactated Ringer's solution and Plasma-Lyte A together, and this trial does not inform the choice between the two.

Subgroup	Balanced Crystalloids	Saline	Odds Ratio (95% CI)	P Value	P Value for Interaction
	no. of events/total no. (%)				
Unit					0.27
Medical	615/2735 (22.5)	659/2646 (24.9)	0.87 (0.77–0.99)	0.04	
Cardiac	202/1470 (13.7)	190/1501 (12.7)	1.10 (0.89–1.36)	0.38	
Neurologic	116/1440 (8.1)	141/1377 (10.2)	0.77 (0.59–0.99)	0.04	
Trauma	131/1640 (8.0)	142/1688 (8.4)	0.95 (0.74–1.21)	0.66	
Surgical	75/657 (11.4)	79/648 (12.2)	0.93 (0.66–1.30)	0.66	
Sepsis					0.06
No	744/6775 (11.0)	756/6691 (11.3)	0.96 (0.86–1.07)	0.47	
Yes	395/1167 (33.8)	455/1169 (38.9)	0.80 (0.67–0.94)	0.01	
Traumatic brain injury					0.24
No	1034/7244 (14.3)	1118/7195 (15.5)	0.89 (0.81–0.98)	0.01	
Yes	105/698 (15.0)	93/665 (14.0)	1.09 (0.81–1.47)	0.58	
Categories of kidney function					0.19
Normal	476/5596 (8.5)	514/5561 (9.2)	0.91 (0.80–1.04)	0.16	
Acute kidney injury	315/574 (54.9)	316/537 (58.8)	0.85 (0.67–1.08)	0.18	
Chronic kidney disease	301/1388 (21.7)	307/1360 (22.6)	0.95 (0.79–1.13)	0.55	
Previous renal-replacement therapy	47/384 (12.2)	74/402 (18.4)	0.61 (0.41–0.91)	0.01	
Overall	1139/7942 (14.3)	1211/7860 (15.4)	0.91 (0.83–0.99)	0.04	

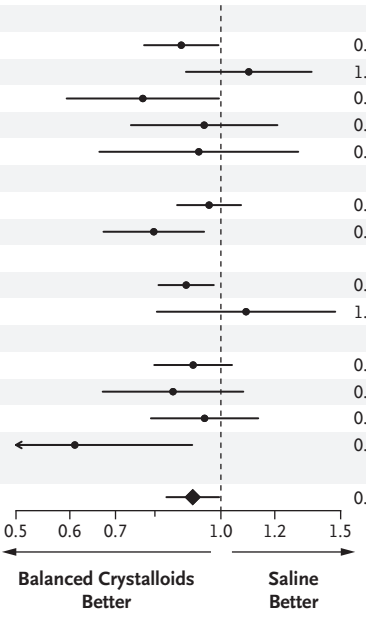


Figure 3. Subgroup Analysis of Rates for the Composite Outcome of Death, New Receipt of Renal-Replacement Therapy, or Persistent Renal Dysfunction.

The odds ratio and 95% confidence interval are shown overall and according to subgroup for the percentage of patients in the balanced-crystalloids group and the saline group who met the criteria for the composite outcome of death from any cause, new renal-replacement therapy, or persistent renal dysfunction. Normal kidney function refers to patients who had no acute kidney injury, chronic kidney disease, or renal-replacement therapy before enrollment. Acute kidney injury refers to patients without chronic kidney disease whose first creatinine level after enrollment was at least 200% of the baseline value or was both greater than 4.0 mg per deciliter (350 μmol per liter) and had increased at least 0.3 mg per deciliter (27 μmol per liter) from the value at baseline.[22] Chronic kidney disease refers to patients with a glomerular filtration rate less than 60 ml per minute per 1.73 m^2 as calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation with the value for the patient's baseline creatinine level.[25] Previous renal-replacement therapy refers to patients known to have received any form of renal-replacement therapy before enrollment.

In conclusion, in this trial involving critically ill adults, intravenous administration of balanced crystalloids rather than saline had a favorable effect on the composite outcome of death, new renal-replacement therapy, or persistent renal dysfunction.

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ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Noncritically Ill Adults

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ABSTRACT

BACKGROUND

Comparative clinical effects of balanced crystalloids and saline are uncertain, particularly in noncritically ill patients cared for outside an intensive care unit (ICU).

METHODS

We conducted a single-center, pragmatic, multiple-crossover trial comparing balanced crystalloids (lactated Ringer's solution or Plasma-Lyte A) with saline among adults who were treated with intravenous crystalloids in the emergency department and were subsequently hospitalized outside an ICU. The type of crystalloid that was administered in the emergency department was assigned to each patient on the basis of calendar month, with the entire emergency department crossing over between balanced crystalloids and saline monthly during the 16-month trial. The primary outcome was hospital-free days (days alive after discharge before day 28). Secondary outcomes included major adverse kidney events within 30 days — a composite of death from any cause, new renal-replacement therapy, or persistent renal dysfunction (defined as an elevation of the creatinine level to ≥200% of baseline) — all censored at hospital discharge or 30 days, whichever occurred first.

RESULTS

A total of 13,347 patients were enrolled, with a median crystalloid volume administered in the emergency department of 1079 ml and 88.3% of the patients exclusively receiving the assigned crystalloid. The number of hospital-free days did not differ between the balanced-crystalloids and saline groups (median, 25 days in each group; adjusted odds ratio with balanced crystalloids, 0.98; 95% confidence interval [CI], 0.92 to 1.04; P=0.41). Balanced crystalloids resulted in a lower incidence of major adverse kidney events within 30 days than saline (4.7% vs. 5.6%; adjusted odds ratio, 0.82; 95% CI, 0.70 to 0.95; P=0.01).

CONCLUSIONS

Among noncritically ill adults treated with intravenous fluids in the emergency department, there was no difference in hospital-free days between treatment with balanced crystalloids and treatment with saline. (Funded by the Vanderbilt Institute for Clinical and Translational Research and others; SALT-ED ClinicalTrials.gov number, NCT02614040.)

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A Quick Take is available at NEJM.org

Administration of intravenous isotonic crystalloids is one of the most common medical therapies, with routine use in emergency departments, hospital wards, intensive care units (ICUs), and operating rooms.[1] However, it is not known whether the composition of isotonic crystalloid fluid has an effect on patient outcomes.[1-3] In the United States, saline (0.9% sodium chloride; "normal saline") is the most commonly used isotonic crystalloid, with more than 200 million liters administered annually.[1] The chloride concentration of saline (154 mmol per liter) is higher than that of human plasma (94 to 111 mmol per liter). Infusion of saline generally causes hyperchloremic metabolic acidosis and may increase renal inflammation and impair renal perfusion.[4-8] Although the clinical significance of these physiological effects is incompletely understood, accumulating evidence suggests that the supraphysiologic chloride concentration of saline may contribute to kidney injury and impair a patient's ability to recover from severe illness.[9-15] The chloride concentration in physiologically balanced crystalloids, such as lactated Ringer's solution (109 mmol per liter) and Plasma-Lyte A (98 mmol per liter), are more similar to that of human plasma.[1,2]

Previous clinical studies that compared balanced crystalloids and saline have focused on critically ill patients in the ICU and operating room.[9-18] Although critically ill patients may be the most vulnerable to potential detrimental effects of saline, acutely ill patients without organ failure or other critical illness comprise a large patient population that is routinely treated with intravenous fluids.[1,19] Owing to the vast number of noncritically ill patients exposed to crystalloids, even small differences in the absolute risk of kidney injury or death between balanced crystalloids and saline may have large public health implications. In the present trial, we investigated the clinical effect of balanced crystalloids versus saline for routine intravenous fluid therapy in the emergency department among noncritically ill adults. We hypothesized that balanced crystalloids would result in earlier hospital discharge and a lower incidence of major adverse kidney events than saline.

Methods

Trial Design and Oversight

Our trial, the Saline against Lactated Ringer's or Plasma-Lyte in the Emergency Department (SALT-ED) trial, was a single-center, pragmatic, unblinded, multiple-crossover trial that compared balanced crystalloids and saline among consecutive noncritically ill adults treated with intravenous crystalloids in the emergency department before hospitalization outside the ICU. The rationale, design, and statistical analysis plan were prespecified and have been published.[20] The protocol is also available with the full text of this article at NEJM.org. The institutional review board at Vanderbilt University approved the trial with waiver of informed consent. The trial was monitored by an independent data and safety monitoring board.[20] The first and fourth authors vouch for the completeness and accuracy of the data and analyses.

Trial Population

The trial was conducted between January 1, 2016, and April 30, 2017, in the Vanderbilt University Medical Center Adult Emergency Department, a tertiary-care, academic, hospital-based emergency department in the United States with approximately 75,000 visits per year. The trial population consisted of adults (≥18 years old) who received at least 500 ml of intravenous isotonic crystalloids in the emergency department and were subsequently hospitalized outside an ICU. Patients who were admitted to an ICU from the emergency department were defined as critically ill and were enrolled in a separate trial that compared balanced crystalloids and saline among critically ill adults, the Isotonic Solutions and Major Adverse Renal Events Trial (SMART), reported in this issue of the *Journal*.[16] Patients who received less than 500 ml of crystalloids in the emergency department were excluded owing to the low dose of exposure to the intervention.[15] The unit of analysis was unique emergency department visit, with individual patients potentially contributing multiple visits. In a sensitivity analysis, we limited the trial population to the first emergency department visit among unique patients.

Treatment Assignments

The trial protocol guided the type of isotonic crystalloid that was administered in the emergency department. All other aspects of care were determined by treating clinicians independent of the trial protocol, including whether to treat with crystalloids and the volume of crystalloids administered. Consistent with the concept of a pragmatic clinical trial,[21] trial procedures were

embedded within routine care and executed by clinical personnel.

The methods of treatment assignment have been described previously.[20] In brief, the type of isotonic crystalloid was assigned according to calendar month, with all patients in the trial emergency department during the same month assigned to the same fluid, either balanced crystalloids or saline. During balanced-crystalloids months, clinicians had the option of choosing either lactated Ringer's solution or Plasma-Lyte A. Clinicians and patients were aware of the treatment assignments. The first trial month was assigned by means of computer-generated simple randomization. Treatment assignments then sequentially crossed over between balanced crystalloids and saline each month for a total of 16 months (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Selection of fluids after the patient's transfer from the emergency department to a hospital floor was not included as part of the trial intervention.

Electronic advisors within the electronic order-entry system informed providers about the trial, asked about relative contraindications to the assigned crystalloid, and guided them through crystalloid orders.[20] Relative contraindications to the use of balanced crystalloids included hyperkalemia and brain injury; the severity of hyperkalemia and brain injury at which saline was used instead of balanced crystalloids was determined by the treating provider. There were no relative contraindications listed for saline in the electronic advisor. Providers had the option of ordering off-protocol crystalloids if they believed an alternative was specifically indicated. Patients who received off-protocol fluids were included in the primary analysis according to intention-to-treat principles. In a secondary per-protocol analysis, the population was limited to patients who received all fluids in accordance with the protocol.

DATA COLLECTION

Data were extracted from the electronic medical record. We have previously validated these data-collection techniques for relevant data points.[15,22,23] Coexisting conditions at baseline were summarized with the Elixhauser Comorbidity Index score.[24]

OUTCOMES

The primary outcome was hospital-free days to day 28, a composite of in-hospital death and hospital length of stay defined as the number of days alive and out of the hospital between the index emergency department visit and 28 days later.[20,25] Patients who died during the index hospitalization and those hospitalized for more than 28 days were classified as having zero hospital-free days. For patients discharged alive before day 28, hospital-free days were calculated as 28 minus length of stay.

The trial included three key secondary outcomes: major adverse kidney events within 30 days, acute kidney injury of stage 2 or higher, and in-hospital death. Major adverse kidney events within 30 days was a composite of death, new renal-replacement therapy, or persistent renal dysfunction (final serum creatinine concentration, ≥200% of the baseline value) at the earliest of hospital discharge or 30 days after the index emergency department visit (Table S1 in the Supplementary Appendix).[26] Stage 2 or higher acute kidney injury was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) creatinine criteria as a maximum serum creatinine concentration at least 200% of the baseline value, an increase in the serum creatinine concentration to at least 4 mg per deciliter (354 μmol per liter) with an absolute increase of at least 0.5 mg per deciliter (44 μmol per liter), or initiation of new renal-replacement therapy before the earliest of hospital discharge or 30 days after the index emergency department visit.[27] In-hospital death was defined as death before hospital discharge, regardless of hospital length of stay.

Patients with end-stage renal disease who were receiving long-term renal-replacement therapy at presentation were not eligible to meet renal outcomes, including new renal-replacement therapy, persistent renal dysfunction, and acute kidney injury. However, patients with end-stage renal disease could meet the outcome of major adverse kidney events within 30 days through death. The baseline creatinine value was defined as the lowest recorded value within the electronic medical record at the trial institution in the year before presentation in the emergency department. Patients with no recorded creatinine values in the previous year had a baseline creatinine value calculated under the assumption of normal baseline renal function with the use of the following equation: [creatinine (in milligrams per deciliter) = 0.74 − 0.2 (if patient is female) + 0.08 (if patient is black) + 0.003 × age (in years)].[28] The serum creatinine concentration in the emergency department was defined as the first re-

corded value during the index emergency department visit. Creatinine values in the emergency department were considered to be baseline characteristics, whereas creatinine values after hospital admission were considered outcomes. Major adverse kidney events within 30 days and acute kidney injury were calculated on the basis of creatinine values after admission. Patients who presented to the emergency department with a creatinine value that met the criteria for acute kidney injury and who then had a drop in creatinine such that no value after hospital admission met these criteria did not have an outcome of acute kidney injury for the purposes of this trial. Additional, exploratory outcomes are described in Table S2 in the Supplementary Appendix.

STATISTICAL ANALYSIS

A trial duration of 16 months was selected to ensure numerous alternating periods of balanced crystalloids and saline, enrollment throughout the academic and calendar year, coordination with the concomitant trial (SMART),[16] and adequate sample size (power) to balance baseline characteristics and detect at least a 0.5-day difference in hospital-free days between groups. Sample size was dependent on the number of patients treated with isotonic crystalloids in the trial emergency department and hospitalized outside an ICU during the 16-month trial period. All the patients who met these criteria were enrolled. On the basis of historical data from the trial emergency department, we estimated that approximately 14,000 patients would be enrolled in 16 months, with the saline group having a mean (±SD) of 24±4 hospital-free days. Under these assumptions, 14,000 patients would provide more than 90% power to detect a difference of 0.5 hospital-free days between groups with a type I error rate of 0.05. One interim analysis was completed by the data and safety monitoring board at the midpoint of enrollment, which resulted in a recommendation to continue enrollment for the planned 16 months.[20]

An intention-to-treat analysis of eligible patients who were assigned to balanced crystalloids or saline was completed for the primary and secondary outcomes. Hospital-free days were analyzed with a multivariable proportional-odds model. Major adverse kidney events within 30 days, acute kidney injury, and in-hospital death were analyzed with multivariable logistic-regression models. Each model was adjusted for the following baseline characteristics: age, sex, race, admitting inpatient service, and days elapsed since the initiation of the trial.[20]

Heterogeneity of treatment effect was evaluated by adding an interaction term[29] to the models between trial-group assignment and each of the following prespecified baseline characteristics: serum creatinine, chloride, and bicarbonate concentrations in the emergency department; age; hospital admission service; and volume of crystalloid administered in the emergency department. A per-protocol secondary analysis was performed that included patients treated exclusively with the assigned crystalloid in the emergency department (100% adherence to trial treatment assignments).

A two-sided P value of less than 0.049 was considered to indicate statistical significance for the primary outcome after we accounted for one interim analysis with a Haybittle–Peto boundary of less than 0.001. With the use of the Bonferroni approach, a two-sided P value of less than 0.017 was considered to indicate statistical significance for the three key secondary outcomes: major adverse kidney events within 30 days, acute kidney injury, and in-hospital death. Analyses were conducted with R software, version 3.2.0 (R Foundation for Statistical Computing), and STATA software, version 14 (StataCorp).

RESULTS

PATIENTS

During the 16-month trial, 19,949 patients were treated with isotonic crystalloids in the emergency department and hospitalized; 3689 patients received less than 500 ml of crystalloids and were excluded, whereas 2913 patients were admitted from the emergency department to an ICU and enrolled in SMART[16] (Fig. S2 in the Supplementary Appendix). The final sample size was 13,347 patients, including 6708 (50.3%) assigned to balanced crystalloids and 6639 (49.7%) assigned to saline. Baseline creatinine values were calculated for 4666 patients (35.0%) who did not have an available measured value. Baseline characteristics were similar between the two groups, including demographic characteristics, burden of coexisting conditions, admitting service, and renal function (Table 1).

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Balanced Crystalloids (N=6708)	Saline (N=6639)
Median age (IQR) — yr	54 (37–67)	53 (37–67)
Female sex — no. (%)	3507 (52.3)	3379 (50.9)
Race — no. (%)†		
White	5159 (76.9)	5189 (78.2)
Black	1335 (19.9)	1251 (18.8)
Other	214 (3.2)	199 (3.0)
Median Elixhauser Comorbidity Index score (IQR)‡	7 (3–14)	7 (3–14)
Admission service — no. (%)		
Medicine services		
General medicine	4747 (70.8)	4687 (70.6)
Cardiology	303 (4.5)	321 (4.8)
Neurology	117 (1.7)	144 (2.2)
Surgery services		
General surgery	1278 (19.1)	1211 (18.2)
Trauma	263 (3.9)	276 (4.2)
Median baseline serum creatinine (IQR) — mg/dl	0.84 (0.71–0.95)	0.85 (0.71–0.94)
Source of baseline creatinine — no. (%)		
Measured value in medical record	4405 (65.7)	4276 (64.4)
Calculated value by equation	2303 (34.3)	2363 (35.6)
Initial kidney function in ED		
Serum creatinine		
Mean — mg/dl	1.32±1.42	1.31±1.36
Median (IQR) — mg/dl	0.93 (0.77–1.33)	0.93 (0.77–1.32)
≥1.5 mg/dl — no. (%)	1246 (18.6)	1240 (18.7)
End-stage renal disease with long-term renal-replacement therapy — no. (%)	126 (1.9)	109 (1.6)
Stage 2 or higher acute kidney injury — no./total no. (%)§	643/6582 (9.8)	631/6530 (9.7)
Initial serum electrolytes in ED		
Sodium — mmol/liter	137.2±4.2	137.4±4.3
Chloride — mmol/liter	102.8±5.4	103.1±5.6
Potassium — mmol/liter	4.1±0.7	4.1±0.7
Bicarbonate — mmol/liter	22.7±3.8	22.8±3.7
Blood urea nitrogen — mg/dl	20±16	20±16

* Plus–minus values are means ±SD. There were no significant differences in baseline characteristics between the two groups, except for initial serum sodium (P=0.006) and chloride (P=0.003). To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357. ED denotes emergency department, and IQR interquartile range.

† Race was reported by patients or their surrogates and recorded in the electronic health record as a part of routine clinical care.

‡ The Elixhauser Comorbidity Index score summarizes the burden of a patient's coexisting conditions. Scores range from −19 to 89, with higher scores indicating a profile of coexisting conditions that is more strongly associated with in-hospital death.[24]

§ Acute kidney injury was defined according to the Kidney Disease: Improving Global Outcomes creatinine criteria. Patients with end-stage renal disease who were receiving long-term renal-replacement therapy at the time of ED arrival were not eligible for the outcome of acute kidney injury.

Table 2. Crystalloids Received in the Emergency Department According to Assigned Treatment Group.*

Variable	Balanced Crystalloids (N=6708)	Saline (N=6639)
Total crystalloid volume		
Mean — ml	1608±1095	1597±1105
Median (IQR) — ml	1089 (1000–2000)	1071 (1000–2000)
≥2000 ml — no. (%)	2207 (32.9)	2150 (32.4)
Median volume of balanced crystalloids (IQR) — ml	1000 (1000–2000)	0
Median volume of saline (IQR) — ml	0	1000 (1000–2000)
Percentage of crystalloid volume consistent with assigned group — no. (%)		
100%: per-protocol population	5620 (83.8)	6160 (92.8)
51–99%	514 (7.7)	270 (4.1)
1–50%	254 (3.8)	131 (2.0)
0%	320 (4.8)	78 (1.2)

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding.

CRYSTALLOID TREATMENT

Patients received a median crystalloid volume of 1079 ml (interquartile range, 1000 to 2000). Most balanced crystalloids were administered as lactated Ringer's solution (95.3%), with a small percentage administered as Plasma-Lyte A (4.7%). Overall, 88.3% of the patients received only the assigned crystalloid in the emergency department with no use of off-protocol crystalloids. The volume of crystalloid that was administered and the adherence to crystalloid assignment were similar in the balanced-crystalloids and saline groups (Table 2, and Fig. S3 in the Supplementary Appendix).

SERUM ELECTROLYTE CONCENTRATIONS

After treatment with intravenous fluids in the emergency department, patients in the balanced-crystalloids group had lower chloride and higher bicarbonate concentrations than those in the saline group; these differences persisted for several days into the hospitalization (Fig. 1). Hyperchloremia (serum chloride concentration, >110 mmol per liter) and acidemia (serum bicarbonate concentration, <20 mmol per liter) were less common after treatment with balanced crystalloids than with saline (Table S3 in the Supplementary Appendix).

INTENTION-TO-TREAT ANALYSIS

There was no difference in the number of hospital-free days between patients in the balanced-crystalloids and saline groups (median, 25 days in each group; adjusted odds ratio with balanced crystalloids, 0.98; 95% confidence interval [CI], 0.92 to 1.04; P=0.41) (Table 3, and Fig. S4 in the Supplementary Appendix). Patients in the balanced-crystalloids group had a lower incidence of major adverse kidney events within 30 days than those in the saline group (4.7% vs. 5.6%; adjusted odds ratio, 0.82; 95% CI, 0.70 to 0.95; P=0.01). A lower count for each component of major adverse kidney events — death, renal-replacement therapy, and persistent renal dysfunction — in the balanced-crystalloids group contributed to the lower incidence of the composite outcome (Table 3, and Fig. S5 in the Supplementary Appendix). Stage 2 or higher acute kidney injury occurred in 8.0% of patients in the balanced-crystalloids group and 8.6% of patients in the saline group (adjusted odds ratio, 0.91; 95% CI, 0.80 to 1.03; P=0.14). Other clinical outcomes did not differ significantly between the two groups (Table S3 in the Supplementary Appendix).

HETEROGENEITY OF TREATMENT EFFECT

Hospital-free days were similar for patients in the balanced-crystalloids and saline groups across a

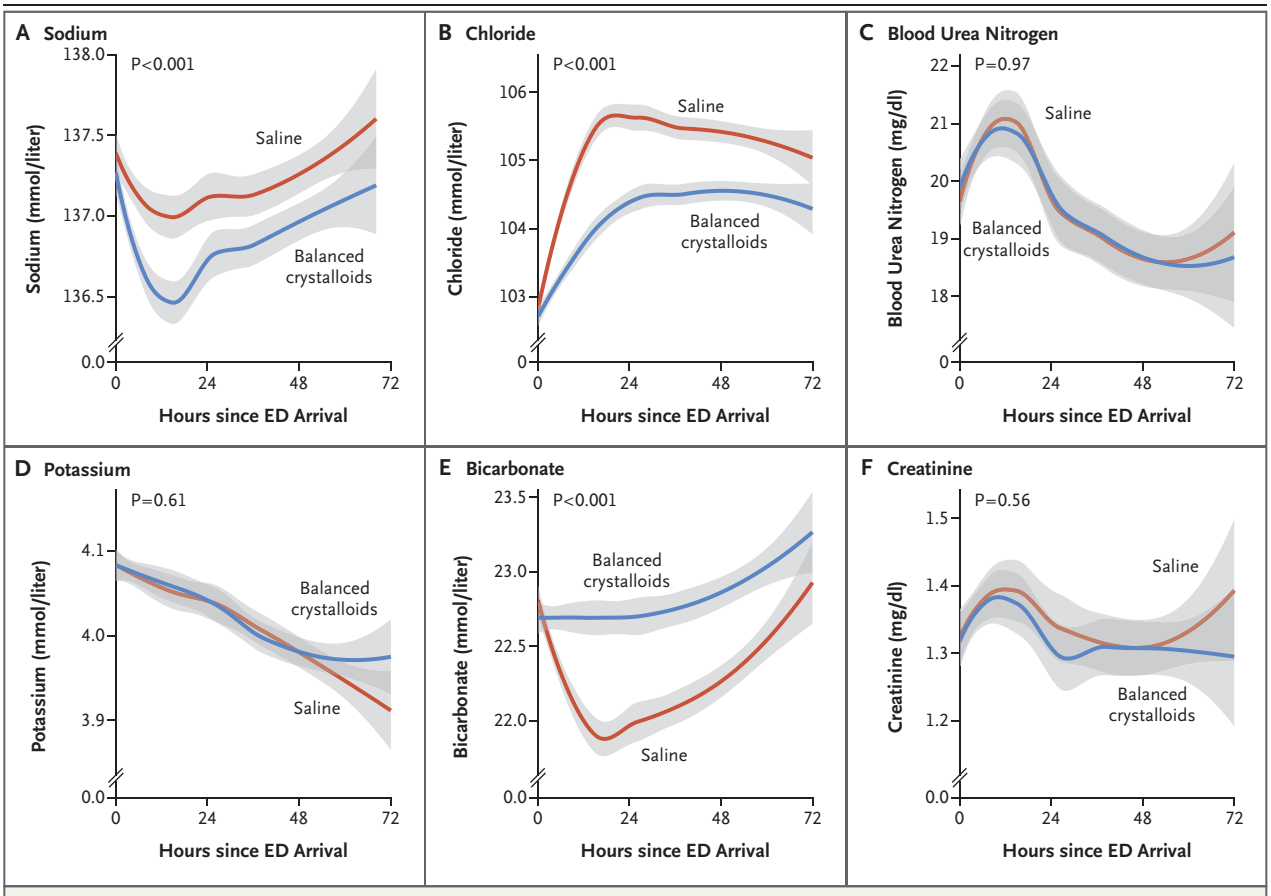

Figure 1. Serum Electrolyte Concentrations in the First 72 Hours after Arrival in the Emergency Department (ED).

Lines and bands represent means and 95% confidence intervals, respectively. Plots were generated with the use of locally weighted scatterplot smoothing. The P values in the figure represent the overall difference between groups, calculated with the use of proportional-odds models. Over time, the separation between groups increased for chloride (P<0.001 for interaction) and bicarbonate (P<0.001 for interaction); interaction terms for the other variables were not significant. To convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

broad range of baseline characteristics (Fig. 2). Patients who presented to the emergency department with renal dysfunction (serum creatinine concentration, ≥1.5 mg per deciliter [133 μmol per liter]) or hyperchloremia (serum chloride concentration, >110 mmol per liter) appeared to have the largest benefit from balanced crystalloids for avoiding major adverse kidney events within 30 days and acute kidney injury. Among patients who presented to the emergency department meeting KDIGO criteria for stage 2 or higher acute kidney injury (1274 patients), resolution of acute kidney injury during hospitalization was more common with balanced crystalloids, as shown by a lower incidence of major adverse kidney events within 30 days in the balanced-crystalloids group (28.0%) than in the saline group (37.6%) (P<0.001).

SENSITIVITY AND PER-PROTOCOL ANALYSES

Sensitivity analyses that were adjusted for period effect and that limited the trial population to patients without end-stage renal disease at presentation in the emergency department (13,112 patients), to patients with a measured baseline serum creatinine value (8681 patients), and to the first emergency department visit among unique patients in the trial (10,573 patients) all produced results similar to those of the primary analysis (Table S4 in the Supplementary Appendix).

Table 3. Clinical Outcomes According to Assigned Treatment Group in the Intention-to-Treat Analysis.

Outcome	Balanced Crystalloids (N=6708)	Saline (N=6639)	Adjusted Odds Ratio (95% CI)*	Adjusted P Value
Median hospital-free days to day 28 (IQR)	25 (22–26)	25 (22–26)	0.98 (0.92–1.04)	0.41
Major adverse kidney event within 30 days — no. (%)	315 (4.7)	370 (5.6)	0.82 (0.70–0.95)	0.01
Death — no. (%)	94 (1.4)	102 (1.5)	0.89	
New renal-replacement therapy — no./total no. (%)†	18/6582 (0.3)	31/6530 (0.5)	0.56	
Final serum creatinine ≥200% of baseline — no./total no. (%)†	253/6582 (3.8)	293/6530 (4.5)	0.84	
Stage 2 or higher acute kidney injury — no./total no. (%)†	528/6582 (8.0)	560/6530 (8.6)	0.91 (0.80–1.03)	0.14
In-hospital death — no. (%)	95 (1.4)	105 (1.6)	0.88 (0.66–1.16)	0.36

* Multivariable models were adjusted for age, sex, race, admitting service, and time (days since trial initiation).
† Patients with end-stage renal disease who were receiving long-term renal-replacement therapy at the time of emergency department arrival (126 in the balanced-crystalloids group and 109 in the saline group) were not eligible for the following outcomes: new renal-replacement therapy within 30 days, final serum creatinine concentration within 30 days at least 200% of the baseline value, and stage 2 or higher acute kidney injury.

The per-protocol analysis (11,780 patients) also produced similar results (Tables S5 and S6 in the Supplementary Appendix).

DISCUSSION

In this pragmatic trial of noncritically ill adults treated with intravenous fluid in the emergency department, treatment with balanced crystalloids did not result in a shorter time to hospital discharge (hospital-free days) than treatment with saline but did result in a lower incidence of the composite of death, new renal-replacement therapy, and persistent renal dysfunction (major adverse kidney events within 30 days), which was a secondary outcome. The lower incidence of major adverse kidney events within 30 days in the balanced-crystalloids group is consistent with the results of SMART, which was conducted concurrently in critically ill adults.[16]

Patients in the present trial had lower risks of renal outcomes and death overall than critically ill adults requiring ICU admission.[10,15,16,30] Despite these lower risks, there was an absolute difference of 0.9 percentage points in the risk of major adverse kidney events within 30 days in favor of the balanced-crystalloids group, corresponding to a number needed to treat of 111. Although this risk difference is modest for each patient, implications on a population level may be substantial owing to the millions of patients who receive isotonic crystalloids annually.[1,19] Operationally, lactated Ringer's solution and saline are similar in terms of cost, availability, and procedures for administration.[2,31]

A strength of our trial was high adherence to the assigned crystalloid group. Use of an unblinded, pragmatic design in a learning health care system[32] facilitated incorporation of the trial into routine practice, allowing the assigned crystalloid to be systematically used for early fluid resuscitation immediately after arrival in the emergency department.

Limitations of the trial include its single-center setting, unblinded design, and outcome ascertainment that was limited to the index hospitalization. Owing to the pragmatic design that used data collection from the electronic medical record, more detailed information about patient characteristics was not available. In addition, crystalloids used for intravenous fluid therapy in the emergency department were included in the trial intervention, but fluids administered after hospital admission and those used as medication carriers were not controlled. Lactated Ringer's solution represented more than

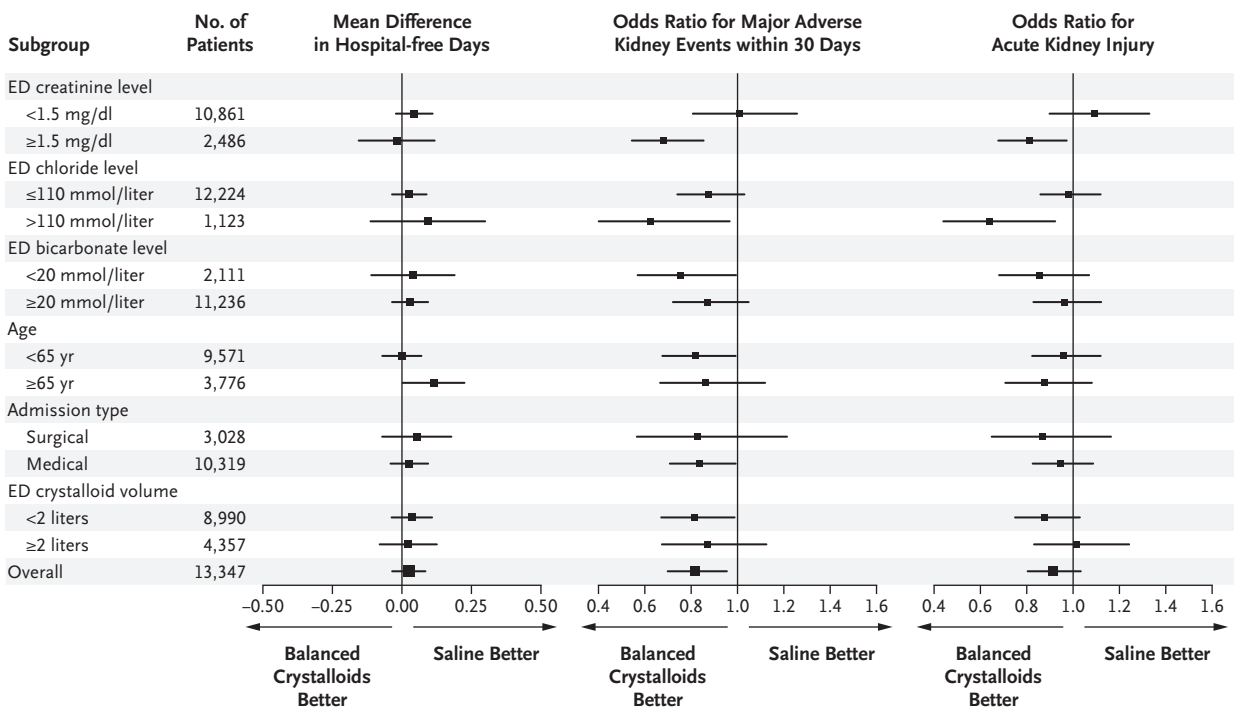

Figure 2. Heterogeneity of Treatment Effect.

Shown are forest plots for hospital-free days to day 28, major adverse kidney events within 30 days, and acute kidney injury of stage 2 or higher according to Kidney Disease: Improving Global Outcomes creatinine criteria. The outcome of major adverse kidney events within 30 days was a composite of death from any cause, new renal-replacement therapy, or persistent renal dysfunction (defined as an elevation of the creatinine level to ≥200% of baseline) — all censored at hospital discharge or 30 days, whichever occurred first. Patients with end-stage renal disease who were receiving long-term renal-replacement therapy at the time of arrival in the emergency department (235 patients) were not eligible for the outcome of acute kidney injury; hence, the total sample size for the analysis of acute kidney injury was 13,112.

95% of the balanced crystalloids used in the trial; additional study is required to compare Plasma-Lyte A with both saline and lactated Ringer's solution. Last, this trial evaluated balanced crystalloids versus saline as the routine, first-line isotonic fluid in a broad patient population; fluid selection that is tailored to specific patient characteristics is an alternative approach that was not evaluated in this trial.

In conclusion, in this pragmatic clinical trial involving noncritically ill adults treated with intravenous fluids in the emergency department, the number of hospital-free days, the primary outcome of the trial, did not differ between patients assigned to balanced crystalloids and those assigned to saline.

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Clinical paper

Early ECPR for out-of-hospital cardiac arrest: Best practice in 2018

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ABSTRACT

Extracorporeal CPR is a second line treatment for refractory cardiac arrest, as written in the latest International Guidelines. Optimal timing, patient selection, location and method of implementation vary across the world. The objective here is to present an international consensus on the pillars of an ECPR program. The major aspect the group agrees on in that ECPR should be implemented within 60 minutes of collapse. With this in mind, the program should be built according to local resources knowing that the optimal team will require pre-established specific roles with personnel dedicated to resuscitation and others to ECPR.

Introduction

Approximately 500 000 people in Europe sustain cardiac arrests every year (1). The major aetiology (84–99%) of cardiac arrest cases presenting to the Emergency Department (ED) is medical cause (e.g. myocardial infarction). The overall 1-year survival rate for out-of-hospital cardiac arrest remains low (< 6%) [1].

Persistently poor overall survival has triggered interest in a modified approach to cardiac arrest integrating extra-corporeal support of oxygenation and pump function as a second line of treatment. Extracorporeal Cardiopulmonary Resuscitation (ECPR) is salvage therapy for patients suffering cardiac arrest refractory to conventional resuscitation. ECPR provides bridge therapy that maintains organ perfusion whilst the underlying aetiology of the cardiac arrest is determined and treated. In-hospital cardiac arrest (IHCA), treated with ECPR, has recently shown promising survival rates ranging from 20 to 45% [2,3]. Outcomes in patients presenting with refractory out-of-hospital cardiac arrest (OHCA) have been worse [4] – Table 1 lists comparative data from key studies. However, ECPR appears in the latest guidelines in the management of OHCA. Better outcomes after in-hospital cardiac arrest have been attributed to more rapid and effective resuscitation, as well as earlier access to ECPR where that was deployed. Additionally, in studies where subsequent ECPR was deployed, the duration of conventional cardiopulmonary resuscitation (CPR) also appears to impact adversely on outcome [5]. The difference in survival for OHCA and IHCA treated by ECPR disappears after adjustment for the low-flow time [5,6]. Consequently, a system-wide approach to improving cardiac arrest survival and improving access to ECPR should take into consideration minimizing low-flow times. Several studies have shown success with ECPR in the cardiac catheterization laboratory (CCL), emergency department (ED), and in the prehospital environment [5,7–9]. However, as shown in two very recent reviews, ECPR programs lack standardization of care and vary considerably across centres [10,11]. We present an international multi-centre consensus on the fundamental pillars of an ECPR Program for patients who sustain an OHCA

Timing and patient selection

Until recently, refractory OHCA was defined as cardiac arrest

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Table 1
Key Studies on ECPR for IHCA and OHCA interesting the survival rate.

Author/Journal	Type of study	IHCA/ OHCA	Number of patients	Results on survival
Voicu et al Resuscitation 2018 [24]	Observational, Retrospective Single Centre	IHCA OHCA	46	Survival: 9%
Dennis et al IJC 2017 [25]	Observational, Retrospective Multi-centre	IHCA OHCA	37	Survival: 33% for IHCA vs 37% for OHCA
Kuroki et al Resuscitation 2017 [26]	Prospective cohort Single Centre	OHCA	119	Survival: 9% to 74% according to the low flow
Lamhaut et et Resuscitation 2017 [8]	Retrospective observational Singless Centre	OHCA	156	Survival: 38% survival
Wengenmayer et al Crit Care 2017 [3]	Retrospective registry Single Centre	IHCA OHCA	133	Survival: 18,9% for IHCA vs 8,4 for OHCA (p < 0,04)
Pozzi et al IJC 2016 [27]	Retrospective observational Single Centre	OHCA	68	Survival: 31.5% for shockable vs 0% for non shockable
Choi et al Resuscitation 2015 [28]	Observational, Retrospective Multi-Centre	OHCA	320 ECPR vs 36227 No ECPR	Survival: 9% for ECPR group vs 2% for no ECPR group
Sakamoto et al Resuscitation 2014 [4]	Observational, Prospective Multi-Centre	OHCA	260 ECPR vs 194 no ECPR	Survival: 12,3% for ECPR group vs 1,5% for no ECPR group
Johnson et al Resuscitation 2014 [19]	Observational prospective registry Single Centre	IHCA (in ED) OHCA	26	Survival: 15%
Fagnoulet et al Resuscitation 2013 [29]	Observational, prospective registry Single Centre	IHCA OHCA	24	Survival: 25%
Maekawa et al Crit Care Med 2013 [30]	Observational, prospective registry Single Centre	IHCA OHCA	53 ECPR 109 no ECPR	Survival: 29% for ECPR group vs 8% for no ECPR group
Kagawa et al Circulation 2012 [31]	Observational, Retrospective Multi-Centre	IHCA OHCA	86	Survival : 24% and ECPR + PCI = 33%
Bellezzo et al Resuscitation 2012 [9]	Case series Single Centre	OHCA	8	Survival: 5/8 patients survived
Kagawa et al Resuscitation 2010 [6]	Observational retrospective Single Centre	IHCA OHCA	77	Survival 26% for IHCA vs 10% for OHCA (p = 0,07)
Chen et al Crit CareMed 2008 [14]	Observational, Retrospective Single Centre	IHCA	135	Survival: 34%
Chen et al Lancet 2008 [12]	Observational, Prospective Single Centre	IHCA	59 ECPR 113 no ECPR	Survival : 28,8 % for ECPR vs 12,3% for no ECPR

IHCA: Intra-Hospital Cardiac Arrest/OHCA: Out of Hospital Cardiac Arrest.
ECPR: Extracorporeal Cardio-Pulmonary Resuscitation.

unresponsive to 30 min of conventional care. The decision to switch from conventional CPR to ECPR was therefore often delayed until 30 to 45 min of unsuccessful CPR. These delays resulted in widely variable survival rates.

Compelling evidence suggests that duration of conventional CPR is an independent prognostic factor for refractory OHCA treated by ECPR with longer conventional CPR intervals associated with poorer outcomes; this period of cardiac arrest is referred to as low-flow period [6]. Ideally, ECPR should be initiated within 60 min of onset of cardiac arrest such that the low-flow period is kept less than 60 min [3]. Reynolds, et al, showed that probability of survival with good neurological outcome drops after 16 min of CPR [12]. Kim et al., suggested that the optimal cut-off time to switch from conventional CPR to initiate ECPR is 21 min [13]. ECPR must therefore be anticipated and immediately available in cases where eligible patients have failed to respond to the first 10 min of conventional resuscitation. Beyond that, we suggest that the ECPR cannulation should commence within 20 min of collapse in order to be "on pump" within the shortest possible period from point of decision making to proceed to ECPR.

The most important determinant of outcome remains time to basic life support. Consensus guidelines emphasize that rapidly initiated, high-quality chest compressions influences the efficacy of all other interventions. As such it seems sensible to mandate immediate bystander CPR or a no-flow time < 5 min s as an essential inclusion criteria. The upper age limit for eligibility to ECPR varies but most studies exclude patients older than 75. While a number of studies have shown non-shockable rhythms to be associated with worse outcome following ECPR, no early indicators have been shown to be absolutely predictive as to influence patient selection. Patients with a low flow duration > 90 min s are less likely to benefit from ECPR [3,14]. End-tidal CO_2 ($EtCO_2$) has been studied as a predictor of outcome in cardiac arrest, and $EtCO_2$ < 10 mmHg appears to be a cut-off below which favourable outcome is less likely. Therefore, it seems reasonable to include patients without known major comorbidities, presenting with refractory OHCA, a no-flow state of under 5 min, with a persistent shockable rhythm, and an $EtCO_2$ > 10 mmHg. Most recently, "signs of life" (breathing, Gasp, pupillary reflex, movements) whatever the rhythm, have also emerged as good predictors of outcome in patients who subsequently underwent ECPR [8].

ECPR implementation location

Despite international guidelines, resuscitation processes vary across the world. Similarly, the logistics of ECPR implementation will also likely vary. Some centers advocate a "scoop and run" strategy, with immediate EMS transport of patients to an ECPR-capable facility [9,15]. Alternatively, the "stay and treat" philosophy, using a mobile intensive care unit (MICU) to initiate ECPR on scene of the OHCA, has also been shown to be a viable option [16].

Keeping in mind the necessity to implement ECPR within 60 min of collapse, the best strategy remains to be proven, and may be dependent on variables that are unique to each community. The "scoop and run" strategy, in systems with and without MICU-availability, have demonstrated limitations in rapid initiation of ECPR [15,17]. Established in 2011, a prehospital ECPR program using the MICU, has become the system of choice in Paris, France. This strategy has shown to reduce the low-flow time after OHCA, with similar ECPR initation times, success, and complication rates compared to in-hospital ECPR [8].

ECPR team (Fig. 1 and Photo)

ECPR initiation requires a well-organized and specifically trained team. Additionally, since the ECPR team will be task-focused on the cannulation process, a dedicated resuscitation team leader will need to maintain oversight of the overall effort. The composition of this team will vary depending on local program constraints and respective competencies. We propose the following optimal team composition and role distribution based on a consensus view of the authors:

- Resuscitation Team Leader: Doctor/Advanced Paramedic (Pre-Hospital ECPR)
  - Supervise ACLS interventions
  - Establish airway and intravenous access
  - Liaison with ECPR Team
  - Obtain collateral history and inform familly of planned intervention. (i.e. ECPR)
- Resuscitation Nurse/Paramedic 1:

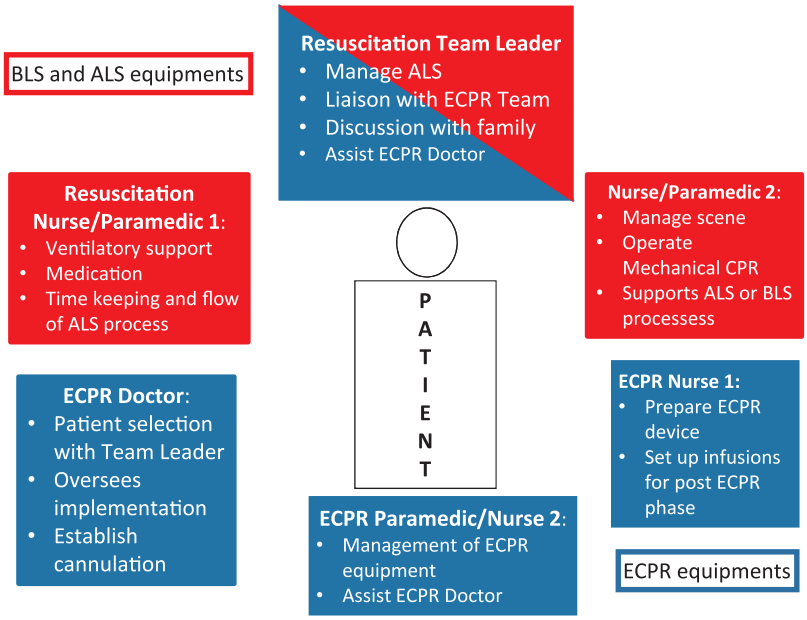

Fig. 1. Organization during an ECPR.

- Provide ventilatory support management
- Deliver medications
- Maintain time-keeping and flow of ALS process

- Paramedic/EMS Technician/Nurse 2:
  - Conduct scene management
  - Operate Mechanical CPR device
- ECPR Doctor:
  - Assist with patient selection for ECPR, in collaboration with the Team Leader
  - Oversee ECPR implementation
  - Perform arterial and venous cannulation
- ECPR Nurse 1:
  - Prepare extracorporeal support circuit
  - Manage post-pump critical care issues
- ECPR Paramedic/Nurse 2:
  - Assist ECPR Doctor
  - Assist EMS with scene management and extrication plan.

ECPR implementation technique/device

Establishing extra-corporeal support after OHCA is time-critical and, as such, a safe well-rehearsed plan is required within a robust overarching clinical governance system. ECPR implementation can be done either percutaneously, through sequential dilatation using standard Seldinger technique [9,18,19], or by direct femoral cutdown [2,5]. A hybrid approach, where cutdown is used to rapidly expose the femoral vessels, vessel access is performed through a distal percutaneous Seldinger technique, and the cutdown site is quickly sutured closed, has also been suggested 8. While each of these techniques have been successfully demonstrated by surgeons, intensivists, anesthesiologists and emergency physicians in multiple reported series, details of each technique is beyond the scope of this paper.

Cannula size is an important component for the efficacy of ECPR. Correct diameter selection of the venous cannula enables adequate drainage of blood from the patient and the diameter of the arterial cannula ensures satisfactory return of flow to the patient. In adults, a

Photo 1. Prehospital ECPR Oganization.

minimum of 21/23 Fr for the venous access and 15/17Fr for the artery is advised, although there is no substantial evidence of the optimal ECPR flow required to maintain vital perfusion. Conversely, one must not lose sight of the complexity and skill required for the cannulation process and distance to an ECPR Centre depending on local resources must also be considered.

The arterial catheter may completely occlude the femoral artery, which is especially problematic with more distal femoral vessel entry. To address this, an anterograde catheter (reperfusion cannula) is connected to the arterial cannula and delivers newly oxygenated blood to the distal extremity on the ipsilateral side to the arterial ECPR cannula. This reperfusion cannulation can be done at the same time as the ECPR arterial cannula insertion or can be delayed to the hospital setting. To avoid ischemic complications to the ipsilateral leg, we recommend the shortest possible interval between ECPR cannulation and placement of the reperfusion catheter. But the time spent for this cannulation need to be balance with the time lost on scene. Placement of the reperfusion catheter can be done through the ECPR cutdown site, or percutaneously with ultrasound guidance.

Peri-ECPR "Resuscitation"

The quality of overall patient care during ECPR, and immediately after ECPR initiation, are crucial to ensure optimal outcomes. The primary objective of ECPR is to increase chances of ROSC but also to improve hemodynamic status while the cause of CA are sought and treated. This has led to the concept of "treatment bundles" to increase neuroprotection and improve prognosis.

The quality of CPR (low-flow state) throughout the entire process leading up to "on pump" phase is critical and as such the use of an automated mechanical chest compression device is recommended to preserve the quality of chest compressions during the transportation to an ECPR centre or during cannulation on-scene. Indeed both are likely to require protracted chest compressions and the former requires significant patient movement that would otherwise require interruption in chest compressions.

Early intubation is recommended for airway protection, strict ventilatory control, and to provide the most accurate EtCO2 values achievable.

Once the decision has been made to initiate ECPR, the treatment strategy and objectives shift from attempting to achieve ROSC to optimizing critical organ perfusion and providing neuroprotection. Administration of drugs (epinephrine and amiodarone), and delivery of defibrillatory shocks, are suspended at this point regardless of rhythm.

Post-ECPR management

Post-ECPR management centers on maintaining adequate organ perfusion and ultimately aims to facilitate the resumption of a native cardiac output or at the very least a pulsatile rhythm. A target mean arterial pressure (MAP) of 60 mmHg and a cautious balance between flow rate and the negative pressure within the venous cannula, is maintained. Fluid boluses may be required to assure adequate intravascular volume to support ECPR. Inotropic agents, such as dobutamine, may be used to off-load the left ventricle, while vasopressor agents (i.e. norepinephrine) maybe used to achieve target MAP. As such, invasive arterial pressure monitoring, as an estimate of the pulsatile rhythm, is indicated in all ECPR cases, and the right radial artery is ideal.

Chest compressions may be discontinued once adequate extracorporeal perfusion has been established. At this time, defibrillation of shockable rhythms is typically more successful after improved coronary perfusion pressure and oxygen-delivery by the extracorporeal pump.

Hyperoxia is problematic after establishment of extracorporeal circulation. Oxygen delivery must be carefully controlled in order to optimize neuroprotection and cardioprotection. The negative effect of hyperoxia was demonstrated on the post resuscitation phase, in patients presenting with STEMI or brain injury [20]. For this reason it seems reasonable to carefully control the oxygen level delivered. A gas mixer, which blends oxygen with air, is used to provide physiologic blood oxygen levels and avoid hyperoxia. Especially in the pre-hospital setting, this point needs logistical anticipation as two gas cylinders, along with the gas blender, are needed. While modification of the percentage of oxygen in the blended gas mixture will affect the arterial oxygen content, gas flow rate (AKA sweep gas rate) affects blood CO2 content.

Treating the presumed cause of the OHCA should be planned as soon as possible. If a STEMI is suspected, the patient should be directed to the CCL for possible percutaneous coronary intervention (PCI). In this population, it has been shown that coronary artery lesions are multiple and proximal [21,22]. The time interval between OHCA and PCI is correlated with survival [23]. If a PE is likely the cause of OHCA, a CT pulmonary angiogram should be considered but minimal pulmonary flow may render this tool of limited value in the absence of a ROSC; echocardiography maybe provide more useful diagnostic clues. Finally, if intracranial hemorrhage is suspected as a precipitant, CT head should precede further interventions.

Program development tips

To be safe and effective, an ECPR program must be prospectively planned and delivered by a highly rehearsed team, with a full understanding of the complexity and risks both to the patient and caregivers (e.g. universal precautions, hazardous materials management, scene logistics, physical heavy lifting demands). The team further requires a shared ethos underpinned by clear clinical practice guidelines on indications, selection criteria, process and management of complications. Within the hospital, a multi-disciplinary approach to the establishment of an ECPR program is vitally important. Intensive care specialists provide ongoing critical care; interventional cardiology may offer PCI in STEMI; interventional radiology may offer services like pulmonary thrombectomy or catheter-directed thrombolysis for PE; and cardiothoracic surgery may offer valuable input to manage intervention complications, cannula management, decannulation or bridge to ventricular assist devices. This multi-disciplinary approach, along with standardization of equipment across the ECPR providers and recipient centres, allows for smooth transitioning of care.

A fundamental component of ECPR program development, in any setting, will be the training program underpinning all tasks performed by team members, alignment to their scope of professional practice and safety-netting with operational guidance that supports delivery. Medium to high fidelity simulation may lend itself well to ECPR team training owing to the complexity of the task and potential gains from repetition, feedback and systematic approach to competencies in this context. The above training, guidance and scope definitions must be protected by an overarching clinical governance framework with multidisciplinary input and review.

Conclusion

ECPR may offer salvage therapy for temporizing management of refractory cardiac arrest with numerous studies now showing a survival benefit that can no longer be ignored.

Providing patients with access to ECPR in a timely manner requires a system-wide approach and engagement, whether implemented in-hospital or in the out-of-hospital setting. We present a multi-centre perspective on challenges encountered and a pragmatic framework that can be adapted to multiple settings.

Ongoing randomized controlled trials on ECPR will hopefully bring additional clarifications to harmonize practices and increase international consensus. The major part of these studies compares an ECPR group to standard care. But some others compare some different strategies to compare ECPR to angioplasty under CA or prehospital

insertion in hospital insertion.

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Isolated traumatic brain injury results in significant pre-hospital derangement of cardiovascular physiology

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ABSTRACT

Introduction: Major trauma can result in both life-threatening haemorrhage and traumatic brain injury (TBI). The pre-hospital management of these conditions, particularly in relation to the cardiovascular system, is very different. TBI can result in cardiovascular instability but the exact incidence remains poorly described. This study explores the incidence of cardiovascular instability in patients undergoing pre-hospital anaesthesia for suspected TBI.
Methods: Retrospective case series of all pre-hospital trauma patients attended by Kent, Surrey & Sussex Air Ambulance Trust (United Kingdom) trauma team during the period 1 January 2015–31 December 2016. Patients were included if they showed clinical signs of TBI, underwent pre-hospital anaesthesia and hospital computed tomography scanning subsequently confirmed an isolated TBI.
Results: Out of 121 patients with confirmed isolated TBI, 68 were cardiovascularly stable throughout the pre-anaesthesia phase, whilst 53 (44%) showed signs of instability (HR > 100bpm and/or SBP < 100 mmHg pre-anaesthesia). Hypotension (SBP < 100) with or without tachycardia was present in 14 (12%) patients. 10 (8%) patients with isolated TBI received pre-hospital blood product transfusion.
Conclusion: Increased awareness that traumatic brain injury can cause significant derangement to heart rate and blood pressure, even in the absence of major haemorrhage, would allow the pre-hospital clinician to treat cardiovascular instability with the most appropriate means, such as crystalloid and vasopressors, to limit secondary brain injury.

Introduction

Major trauma is a significant cause of serious morbidity and mortality, particularly in the young [1]. As haemorrhage is the leading cause of death in trauma, haemodynamic instability in the pre-hospital phase of care is often assumed to be the result of on-going bleeding. A rise in patients' heart rate or fall in their blood pressure is commonly associated with hypovolemic or haemorrhagic shock, but also with obstructive and neurogenic shock. Traditional medical teaching, such as Advanced Trauma Life Support (ATLS) [2], states that isolated traumatic brain injury does not cause shock and that other causes of shock need to be actively sought.

Whilst cardiovascular instability following spinal cord injury is well recognised, the same in the setting of blunt traumatic brain injury (TBI) is less well described [3]. The cardiovascular instability following neurotrauma is poorly understood and felt to be multifactorial. Blunt trauma to the brain, particularly to the insular cortex, can result in catecholamine release and cause neuron-mediated cardiac arrhythmias. Catecholamine release can result in mitochondrial dysfunction, myocyte death and cardiac dysfunction, resulting in hypotension and cardiogenic shock.

Partrick et al. [4], found the incidence of hypotension in paediatric patients with isolated traumatic brain injury to range from 33% (age >12) to 61% (0–5 year old). Mahoney et al. [5] found that isolated traumatic brain injury accounts for 13% of hypotensive episodes after blunt trauma in adult patients.

Acknowledging that isolated TBI may cause cardiovascular instability (tachycardia and/or hypotension) is crucial for delivering the best trauma care to the patient, both in the pre-hospital and hospital phases. Accurately establishing the cause of cardiovascular instability in the pre-hospital phase of trauma care is important, as the clinical interventions are likely to be very different. Patients with haemorrhagic shock may benefit from volume resuscitation

Abbreviations: CT, computed tomography; HEMS, helicopter emergency medical service; HR, heart rate; KSSAAT, Kent, Surrey, Sussex Air Ambulance Trust; PLE, pronounced life extinct; RSI, rapid-sequence induction; SBP, systolic blood pressure; SD, standard deviation; TBI, traumatic brain injury.

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with blood products, whereas those with neurotrauma are likely to need early anaesthesia and vasopressors. Recently, the occurrence of impact brain apnoea and how this can adversely cause cardiovascular instability has been highlighted [6].

Pre-hospital permissive hypotension is often used during the care of a major trauma patient [7], but this would not be the optimal treatment for patients with isolated TBI. It has been shown that isolated episodes of hypotension increases mortality in TBI patients [8]. Pre-hospital emergency medical care aims to prevent secondary brain injury through optimising cerebral perfusion pressure, oxygenation and ventilation. Accurately identifying isolated TBI as a cause of cardiovascular instability could avoid unnecessary blood product transfusion in the pre-hospital setting and allow patient care to be optimised. TBI patients can require pre-hospital anaesthesia, which can significantly affect patient haemodynamics. Having an understanding of the cardiovascular status and the impact TBI may have on this, is therefore important.

In this single centre, retrospective, observational study we sought to evaluate the frequency of cardiovascular instability (defined as heart rate (HR) >100 bpm and/or systolic blood pressure (SBP) <100 mmHg) in major trauma patients with confirmed isolated traumatic brain injury, requiring pre-hospital anaesthesia.

Methods

Kent Surrey and Sussex Air Ambulance Trust (KSSAAT) is a Helicopter Emergency Medical Service (HEMS) covering three counties in the southeast England with a resident population of 4.5 million and transient population of up to 8 million. Two doctor/paramedic teams respond in either a helicopter or response car from two separate bases. The service attends approximately 2000 patients per year. KSSAAT uses a bespoke electronic patient clinical record system (HEMSbase, Medic One Systems Ltd, UK), which includes automated downloading of all pre-hospital physiology data. GCS is assessed by the attending HEMS team and recorded in component parts.

HEMSBase was interrogated for the time period 1 January 2015 to 31 December 2016. Two researchers (MG, MEZ) independently extracted the data and found no significant difference between the datasets. Inclusion criteria were adult (≥17 year old) patients, who underwent pre-hospital rapid sequence induction (RSI) of anaesthesia, had pre-hospital signs of blunt neurotrauma, with isolated TBI subsequently confirmed on hospital computerised tomography (CT) scan. TBI on CT scan was defined as any formally reported radiological abnormality of suspected traumatic origin, other than isolated skull fracture. Paediatric patients were excluded owing to their varying normal cardiovascular physiology ranges and rare incidence of pre-hospital RSI.

We excluded patients who had a suspected medical event leading to traumatic injury, burns, hanging, patients who were pronounced life extinct at the scene and patients whose pre-hospital physiological data were missing. All pre-hospital RSI cases were reviewed. Individual medical records were reviewed to identify patients with pre-hospital cardiovascular instability using heart rate (HR) and systolic blood pressure (SBP). Cardiovascular instability was pragmatically defined as a single pre-RSI episode of either a HR >100bpm and/or SBP <100 mmHg. Patient records were also interrogated for Injury Severity Score (ISS) and mechanism of injury (MOI).

Patients whose CT results were missing or who died in hospital before having CT were allocated to a 'no follow up' group and were excluded from further analysis. Patients with normal CT scan results were allocated to a 'normal CT group' and also excluded from further analysis.

Patients with base of skull fractures were part of the Isolated TBI group, but were excluded from further analysis if CT showed no intracranial pathology other than the fracture. Isolated TBI group was then subdivided into haemodynamically stable patients and those with signs of instability based on heart rate and systolic blood pressure.

This project met National Institute for Healthcare Research (NIHR, UK) criteria for service evaluation and formal ethical approval was therefore not required. The project was approved by the KSSAAT Research & Development Committee and registered as a service evaluation with the University of Surrey.

Results

During this study period, KSSAAT undertook 3873 missions and treated 3485 patients. Patient inclusion is shown in Fig. 1.

Of the 3485 patients, 361 were adult patients who sustained blunt trauma, underwent RSI and pre-hospital signs of blunt neurotrauma. Patients with a medical event leading to minor head injury (GCS14/15 and not deemed to require pre-hospital anaesthesia, n = 25), burns patient (n = 1), hanging (n = 7), patients who were pronounced life extinct (PLE) at the scene (n = 6) and patients with missing physiological data (n = 5) were excluded. This left 317 patients for further analysis.

Of the 317 undergoing pre-hospital anaesthesia, 39 had no follow up data and 22 had a normal CT scan, leaving 256 patients for further analysis. There were 123 patients with confirmed isolated TBI on CT, of which 2 had base of skull fractures with no intracranial pathology, leaving 121(47.6%) patients in the isolated TBI group and 133 (52.4%) patients with polytrauma patients, with or without TBI.

In the Isolated TBI group, mean age was 54.9 years (SD ± 20.7) and median age was 58. In the polytrauma group mean age was 45.1 years (SD ± 21.3) and median was 40. The proportion of each gender was comparable in both groups. Patient demographics are shown in Table 1.

Out of 121 patients with confirmed isolated TBI, 68 were cardiovascularly stable throughout the pre-anaesthesia phase, while 53 (44%) showed signs of instability (HR >100 bpm and/or SBP <100 mmHg pre RSI). Hypotension with or without tachycardia was present in 14 (11.6%) patients. This is shown in Table 2.

Glasgow Coma Score (GCS) was similar in patients undergoing pre-hospital anaesthesia for both traumatic brain injury and polytrauma. The distribution of patients by GCS is shown in Table 3.

Injury Severity Score (ISS) was only available in 71 (59%) of patients with confirmed isolated brain injury. ISS for patients with isolated TBI is presented against pre-anaesthesia cardiovascular status in Table 4.

The most frequent mechanism of injury (MOI) for sustaining isolated TBI was a fall (from standing, from height or down stairs), in 72 (59.5%) cases. The other MOIs were Road Traffic Collisions (RTC), n = 43 (35.5%); assault, n = 4 (3.3%) and crush injury, n = 2 (1.7%). The most frequent MOI among the hypotensive patients with isolated TBI were falls down stairs (4/14) and pedestrian vs motorised vehicle (4/14) as shown in Table 5.

In the cohort, the incidence of isolated TBI was higher in patients over the age of 55, n = 68 (56%). The incidence of haemodynamic instability in relation to age group is shown in Table 6.

Out of 121 patients with isolated TBI, 10 (8.2%) received pre-hospital blood products (lyophilised plasma and/or packed red blood cells), 4 of which were hypotensive (SBP <100). This highlights the difficulty in pre-hospital management and decision making for the patients with vasoactive head injury in prehospital setting.

Discussion

This retrospective, observational study demonstrates that hypotension in the pre-hospital phase following major trauma is relatively common in patients who do not have major haemorrhage.

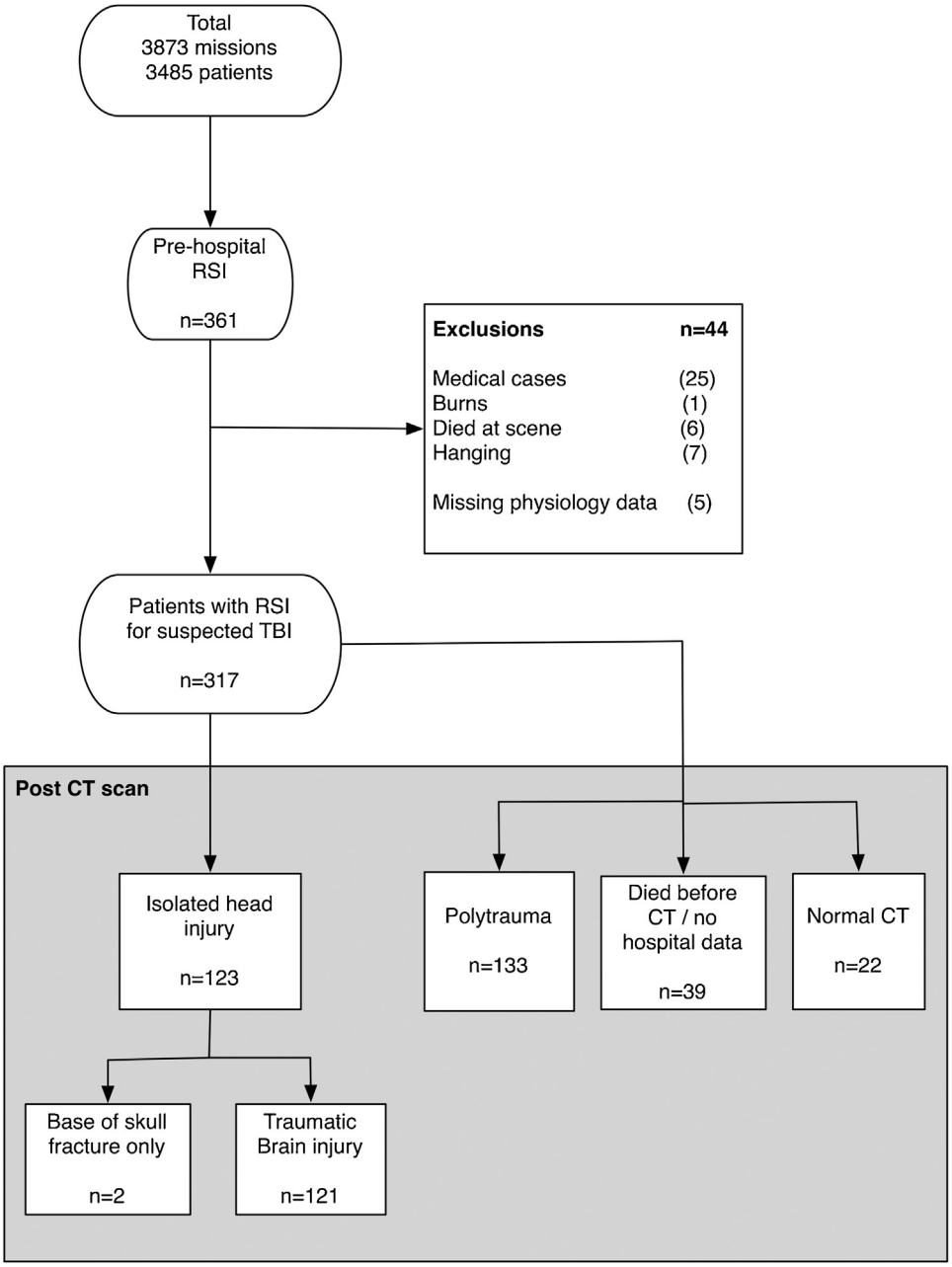

Fig. 1. Patient inclusion flowchart. RSI: rapid sequence induction of anaesthesia; CT: computed tomography scan.

Isolated TBI can result in significant cardiovascular instability and clinicians working in the pre-hospital environment need to be aware of this. We demonstrated that 44% of patients with isolated TBI showed signs of haemodynamic instability (HR >100bpm and/or SBP <100 mmHg), whilst 12% were hypotensive prior to induction of anaesthesia.

This is similar to the results obtained by Mahoney et al. [5], who found that 13% of hypotensive adult trauma patients have isolated brain injury. Chesnut et al. [9] quoted 8.5% in similar study, however this study excluded patients who were dead on arrival to hospital. It could be presumed that some of these deceased patients had a vasoactive head injury, and that inclusion of this deceased group may have resulted in a higher percentage.

An increased awareness of this phenomenon would allow improvement in pre-hospital emergency care. Accurate patient assessment in the pre-hospital environment can be challenging. Every effort should be made to accurately determine the mechanism of injury and undertake meticulous clinical examination to determine whether a cardiovascularly unstable patient has an isolated head injury or polytrauma. Use of pre-hospital ultrasound scanning or point-of-care measurement of blood markers such as lactate, may assist the clinician in determining the true cause of cardiovascular instability. We have shown that cardiovascular instability in TBI can result in inappropriate

Table 1
Demographics of patients undergoing pre-hospital anaesthesia following major trauma.

	Isolated TBI n (%)	Polytrauma n (%)
n (%)	121 (47.6)	133 (52.4)
Age: mean ± SD	54.9 ± 20.7	45.1 ± 21.3
Range	17–94	17–91
Male	92 (76%)	101 (76%)
Female	29 (23%)	32 (24%)

Table 2
Pre-hospital cardiovascular parameters of patients undergoing pre-hospital anaesthesia with subsequently confirmed isolated traumatic brain injury on CT scan. (Cardiovascular unstable patients shown in shaded area).

	HR<100 BP>100	HR>100 BP>100	HR<100 BP<100	HR>100 BP<100
Number of patients	68	39	3	11
%	56.2	32.2	2.5	9.1

Table 3
GCS of patients undergoing pre-hospital emergency anaesthesia.

	Isolated HI unstable	Isolated HI stable	Polytrauma
Mean ± SD	6.64 ± 3.17	7.34 ± 3.13	8.25 ± 4.15
Median	6	7	8
Range	3–15	3–14	3–15

pre-hospital blood product transfusion. In isolated TBI, use of crystalloid fluids and vasopressors would be more appropriate to optimise cardiovascular physiology.

The pathophysiology of neurogenic hypotension or vasoactive head injury is complex and multifactorial. Neurogenic hypotension has been recognised in the last century and demonstrated in animal models using fluid-percussion. Fulton et al. [10] found that brain injury on its own was sufficient to result in hypotension. They suggested that damage to the nuclei in the medulla caused the loss of medullary control of blood pressure, whilst damage to neuronal tracts in hypothalamic region further added to the loss of blood pressure control [10].

Apart from the long standing belief that hypotension results from disruption of brainstem centres for haemodynamic control, there is new understanding of the mechanism of cardiovascular complications of brain injury. TBI induces a catecholamine 'storm' increasing sympathetic outflow, whilst at the same time damage to the insular cortex and hypothalamus results in autonomic dysfunction and a strong pro-inflammatory response causing major adverse effects on the heart [11]. The catecholamine 'storm' results in vasoconstriction, increase cardiac afterload and myocardial oxygen demand, resulting in sub-endocardial ischaemia and impaired ventricular function, which may lead to hypotension [11].

Another pathological feature of TBI is neurogenic stunned myocardium; a reversible, sudden onset, neurologically mediated cardiac dysfunction occurring after various types of acute brain injury as a result of autonomic system imbalance [11,12]. Even though it was initially thought to be due to systemic release of catecholamines, it is now believed to be caused by excessive catecholamine release from myocardial sympathetic nerve endings, resulting in local toxic effects on the myocardium and that it is not related to plasma catecholamine concentration [13].

Table 4
Injury Severity Score of patients with isolated traumatic brain injury undergoing pre-hospital emergency anaesthesia. (Cardiovascular unstable patients shown in shaded area).

ISS	HR<100 BP>100	HR>100 BP>100	BP<100 with or without HR>100
0-9	1	1	0
10-19	6	1	0
20-29	29	13	6
≥30	5	6	3

Table 5
Mechanism of injury (MOI) of patients undergoing pre-hospital anaesthesia with confirmed isolated traumatic brain injury. (Cardiovascular unstable patients shown in shaded area).

MOI	HR<100 SBP>100	HR>100 SBP>100	SBP<100 with or without HR>100
Fall from standing	12	7	2
Fall from height	8	4	1
Fall down stairs	19	15	4
Assault	2	1	1
RTC-cyclist	10	2	0
RTC- motorcyclist	2	4	0
RTC- pedestrian	9	3	4
RTC- 4 or more wheeled vehicle	5	2	2
Crush injury from machinery/injury by object	1	1	0

Table 6
Age distribution of patients undergoing pre-hospital anaesthesia with confirmed isolated traumatic brain injury. (Cardiovascular unstable patients shown in shaded area).

Age	Total	HR<100 SBP>100 (%)	HR>100 SBP>100 (%)	SBP<100 with or without HR>100 (%)
17-25	17	8 (47)	7 (41)	2 (11)
26-40	17	11 (65)	4 (24)	2 (12)
41-55	19	15 (79)	3 (16)	1 (5)
56-70	35	19 (54)	12 (34)	4 (11)
≥71	33	15 (45)	13 (39)	5 (15)

TBI is known to initiate a neuro-inflammatory response leading to the release of mediators, including cytokines, adhesive molecules and others, from the brain into the systemic circulation. This can lead to systemic inflammatory response syndrome (SIRS), causing dysfunction of many organs, including the heart [11]. Supporting the above, Popp et al. [14] found that cardiac index was abnormally low on hospital admission of patients with severe head injury.

Even though our results found a similar frequency of vasoactive head injuries to the other available literature, there are limitations to our study. It is a single centre, retrospective, observational study based on the data available from our electronic database, resulting in missing or incomplete data for number of patients. The significant proportion of patients without follow-up data stems from the difficultly linking hospital and pre-hospital datasets. This is a complex process and hospital follow-up is not always available to our service. Some of the patients in the isolated TBI group also had another minor injury, which was not deemed to affect haemodynamic status. Another limitation is that the group of patients who were tachycardic may have had agitation as a contributing factor, which could clearly influence the results; however, the number of hypotensive patients do not have any similar contributing factors and is deemed to be the true representation of frequency of hypotension in isolated TBI patients following a blunt trauma. We accept that patients with a normal initial CT scan may still have a serious brain injury and that patients with a significant brain injury may not necessarily undergo pre-hospital anaesthesia.

Conclusion

The incidence of pre-hospital cardiovascular instability in patients undergoing pre-hospital anaesthesia with isolated traumatic brain injury was shown to be relatively high, with 44% showing signs of cardiovascular instability (HR >100 bpm and/or SBP <100 mmHg pre-RSI). Hypotension with or without tachycardia was present in 12% of patients. Increased awareness that traumatic brain injury can cause significant derangement to heart rate and blood pressure, even in the absence of major haemorrhage, would allow the pre-hospital clinician to treat cardiovascular instability with the most appropriate means, such as crystalloid and vasopressors, to limit secondary brain injury.

Conflicts of interest

MG, MEZ and RL are all employees of Kent, Surrey & Sussex Air Ambulance Trust. There were no other financial or non-financial conflicts of interest.

Funding

No funding was received for this study.

Authors' contributions

MG and MEZ were involved in data collation and analysis. Data analysis was reviewed by RL. All authors were involved with preparation of the manuscript. All authors approved the manuscript prior to submission.

Ethics

This study met UK National Institute for Health Research criteria for a service evaluation. All the data utilised for this study was routinely collected as part of standard pre-hospital and hospital patient data collection. Formal ethical approval was therefore waived as criteria for service evaluation were met. The study was registered with the University of Surrey as a service evaluation.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analysed during this study are included in this published article.

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Mortality of civilian patients with suspected traumatic haemorrhage receiving pre-hospital transfusion of packed red blood cells compared to pre-hospital crystalloid

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Abstract

Background: Major haemorrhage is a leading cause of mortality following major trauma. Increasingly, Helicopter Emergency Medical Services (HEMS) in the United Kingdom provide pre-hospital transfusion with blood products, although the evidence to support this is equivocal. This study compares mortality for patients with suspected traumatic haemorrhage transfused with pre-hospital packed red blood cells (PRBC) compared to crystalloid.

Methods: A single centre retrospective observational cohort study between 1 January 2010 and 1 February 2015. Patients triggering a pre-hospital Code Red activation were eligible. The primary outcome measure was all-cause mortality at 6 hours (h) and 28 days (d), including a sub-analysis of patients receiving a major and massive transfusion. Multivariable regression models predicted mortality. Multiple Imputation was employed, and logistic regression models were constructed for all imputed datasets.

Results: The crystalloid ($n = 103$) and PRBC ($n = 92$) group were comparable for demographics, Injury Severity Score ($p = 0.67$) and mechanism of injury ($p = 0.73$). Observed 6 h mortality was smaller in the PRBC group ($n = 10$, 10%) compared to crystalloid group ($n = 19$, 18%). Adjusted OR was not statistically significant (OR 0.48, CI 0.19–1.19, $p = 0.11$). Observed mortality at 28 days was smaller in the PRBC group ($n = 21$, 26%) compared to crystalloid group ($n = 31$, 40%), $p = 0.09$. Adjusted OR was not statistically significant (OR 0.66, CI 0.32–1.35, $p = 0.26$). A statistically significant greater proportion of the crystalloid group required a major transfusion ($n = 62$, 60%) compared to the PRBC group ($n = 41$, 40%), $p = 0.02$. For patients requiring a massive transfusion observed mortality was smaller in the PRBC group at 28 days ($p = 0.07$).

Conclusion: In a single centre UK HEMS study, in patients with suspected traumatic haemorrhage who received a PRBC transfusion there was an observed, but non-significant, reduction in mortality at 6 h and 28 days, also reflected in a massive transfusion subgroup. Patients receiving pre-hospital PRBC were significantly less likely to require an in-hospital major transfusion. Further adequately powered multi-centre prospective research is required to establish the optimum strategy for pre-hospital volume replacement in patients with traumatic haemorrhage.

Keywords: Transfusion, Packed Red Blood Cells, Crystalloid, Mortality, Traumatic Haemorrhage, Helicopter Emergency Medical Services

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Background

Traumatic haemorrhage is the leading cause of preventable death in major trauma patients [1, 2]. Approximately half of all patient deaths in the first 24-h are due to haemorrhage [3]. Survival from major traumatic haemorrhage is poor. Trauma patients who require substantial transfusion have a mortality greater than 30 % [4]. National epidemiology studies in England and Wales estimate the annual incidence of major traumatic haemorrhage as 4700 patients, with 1300 patients proceeding to massive haemorrhage [5]. Traumatic haemorrhage is further compounded by coagulopathy [6, 7]. Targeted resuscitation of patients in a post-traumatic coagulopathic state is critical to improving patient outcome [8, 9].

Historically, the hypotensive trauma patient with suspected traumatic haemorrhage was administered crystalloid [10, 11]; however, not without significant adverse effects [6, 12, 13]. Trauma Induced Coagulopathy (TIC) can be sub-divided to endogenous acute traumatic coagulopathy (ATC) and subsequent dilutional coagulopathy [14]. Crystalloid infusion can worsen dilutional coagulopathy [15], endothelial damage and tissue oedema [7], further compounding multiple organ dysfunction and trauma–related bleeding [16, 17]. In-hospital literature highlights worse outcomes for patients receiving greater volumes of crystalloid [18]; negating its administration [11].

Increasingly, Helicopter Emergency Medical Services (HEMS) in the United Kingdom (UK) provide pre-hospital blood product transfusion. Administration of packed red blood cells (PRBC) has emulated from military [19] to civilian practice [20, 21]. The transfusion of PRBC transfusion has become the fluid resuscitation method of choice, and more recently, the addition of freeze dried plasma (FDP) or fresh frozen plasma (FFP) [22]. Early transfusion therapy is postulated to bridge the gap to damage control resuscitation [21, 23]. Literature reports that a delay in transfusion of PRBC (> 10 min) was associated with increased odds of death for transfused patients; supporting expedient transfusion capability [24].

Heterogeneity exists in the UK, with approximately 50% of HEMS services administering blood products versus crystalloid (0.9% sodium chloride) [25]. Equivocal literature, and the combined logistical complexities, storage and clinician availability to provide pre-hospital transfusion of PRBC, has led to widespread heterogeneity across UK HEMS practice. Naumann et al. (25) assert that evidence-based justification of pre-hospital PRBC would see approximately 800 eligible transfusions per year. Despite blood product transfusion being noted as a clinically logical step, PRBC transfusion itself is not without clinical complications. Transfusion reactions, independent association to acute respiratory distress syndrome, incremental infectious complications [26] and multiple organ dysfunction is noted [7, 27].

Clinical literature for the use of pre-hospital PRBC is ambiguous [2, 16]. Systematic review identifies no published prospective, blinded or randomised studies comparing pre-hospital crystalloid and PRBC resuscitation [2, 28]. Furthermore, studies have focused on small patient cohorts highlighting only the feasibility and safety of pre-hospital PRBC transfusion [6, 29–32].

Pre-hospital studies include disparate patient cohorts with confounding interventions and contrasting outcomes [6, 33, 34], which limits meta-analysis [28, 35]. Subsequently, substantial heterogeneity limits long term mortality statistical analysis, this is further hampered by loss to follow up ranging from 18% [36] to 67% [37], respectively. A prospective randomised controlled trial (RCT), Resuscitation with Pre-hospital Blood Products [38] will compare crystalloid (0.9% sodium chloride) against PRBC and FDP, with the primary outcome measures of lactate clearance and all-cause mortality.

To date, clinical literature regarding transfusion of PRBC in civilian patients is equivocal. The objective of this retrospective observational study is to ascertain any association between mortality and patients transfused with pre-hospital PRBC compared to crystalloid (0.9% sodium chloride) in civilian patients with suspected traumatic haemorrhage.

Methods

Study design and pre-hospital care system

This is a single centre, retrospective observational cohort study of patients triggering a pre-hospital ‘Code Red’ activation. The study was registered with the University of Surrey and met UK National Institute of Healthcare Research (NIHR) criteria as a service evaluation. The study applied Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guidelines [39].

The Kent, Surrey and Sussex Air Ambulance Trust (KSSAAT) provides a HEMS service in southeast England, UK. The HEMS clinicians (Physician and Paramedic) deploy by aircraft or response vehicle. Operational teams cover the region over 24 h, with a second team providing operational cover over a further 18 h day. Enhanced medical care is provided to approximately 2000 patients per year in a predominantly rural and static population of 4.5 million, with a transient population of 10 million. Patients were conveyed to one of five Major Trauma Centres (MTC).

Code red standard operating procedure

In this service, where there is a clinical suspicion of major haemorrhage and signs of haemodynamic compromise ‘Code Red’ is declared. Code Red is informed by pre-hospital clinical assessment and declared at the discretion of the attending HEMS clinicians. A Code Red

activation comprised of the following parameters during the study period.

In hypotensive patients with suspected traumatic haemorrhage (systolic blood pressure (SBP) < 80 mmHg or absence of a radial pulse) the concept of 'permissive hypotension' is targeted, i.e. SBP of ≥80 mmHg, or the return of a radial pulse. In patients with polytrauma and suspected traumatic brain injury an SBP of ≥100 mmHg is targeted, and in patients with penetrating torso trauma, a carotid pulse. Alternative causes of hypotension are excluded, such as tension pneumothorax.

From January 2013, following a robust programme of work at KSSAAT, and pragmatic view of available in-hospital and military literature, a decision was made to introduce pre-hospital PRBC transfusion as a clinical logical step in the management of patients with suspected traumatic haemorrhage. A Code Red activation ensured PRBC transfusion through a Belmont Buddy Lite™ fluid warmer (Belmont Instrument Corporation, M. A, USA) and the administration of tranexamic acid. The activation enables a titrated transfusion of up to four units of O Rhesus negative PRBC from the CRĒDO CUBE™ (Series 4, 21 Insulation 15, VIP Golden Hour). Subsequently, a 'pre-alert' call to the receiving hospital triggers a predefined in-hospital major haemorrhage protocol; ensuring blood and clotting factors are immediately available [30, 32]. Adherence and compliance to the Blood Safety and Quality Regulations (2017) [40] and Medicines and Healthcare Regulatory Agency was ensured [41].

Data collection

Between 1 January 2010 and 31 January 2013, Code Red patients were administered crystalloid (*crystalloid group*, sodium chloride 0.9%, in 250 ml boluses titrated to effect). Between 1 February 2013 and 1 February 2015 Code Red patients were transfused with PRBC (*PRBC group*, transfused up to a maximum of 4 units O Rhesus negative PRBC). Paper clinical records were interrogated from January 2010 until July 2013, subsequently a bespoke electronic patient record system was introduced (HEMSBase, Medic One Systems Limited, UK) [42]. HEMSBase was interrogated from July 2013 to February 2015. In February 2015, freeze dried plasma (FDP) was introduced into the service, at this point data collection for eligible patients was ceased.

Patient demographics and clinical data were collected for eligible patients. The SBP (mmHg) reflects the first HEMS recorded value. The recorded volume (mL) of crystalloid is that administered by HEMS clinicians only, and not pre-existing administration by the attending ambulance clinicians. Incident descriptors (mechanism of injury (MOI)), 999 time to HEMS on scene time, and Injury Severity Score (ISS) were reported. Primary outcome of all-cause mortality at 6 h (h) and 28 days (d) was recorded. A sub-analysis of patients receiving in-hospital major transfusion (≥4 units PRBC in 24 h) and massive transfusion (≥10 units PRBC in 24 h), not including pre-hospital PRBC, was reported [15].

Pre-hospital and in-hospital data were reviewed retrospectively. In-hospital data was collected from the Trauma Audit and Research Network (TARN) database. Pre-existing data sharing agreements enabled interrogation of hospital-specific computer-based records for supplementary data. Data was abstracted by the first reviewer (JG); inaccuracies and discrepancies were resolved by a second reviewer (JJ).

Inclusion criteria

Inclusion criteria comprised: 1) blunt and/or penetrating traumatic injury with suspected traumatic haemorrhage, 2) pre-hospital Code Red declaration with transfusion of crystalloid and/or PRBC, 3) patient conveyed to an MTC, 4) traumatic cardiac arrests (TCAs) where return of spontaneous circulation (ROSC) was gained, declared Code Red and conveyed to an MTC.

Exclusion criteria comprised: 1) paediatrics (< 16 years), 2) patients declared Code Red with a suspected medical aetiology, 2) TCA; where patients were pronounced life extinct, 3) patients transferred to non-MTCs, 4) inter-hospital and/or secondary transfers.

Primary outcome measure

The co-primary outcome measures were in-hospital all-cause mortality at 6 h and 28 d. In order to identify patients with 'true' ongoing haemorrhage a sub-analysis of all-cause mortality for patients receiving a massive transfusion or major transfusion over the first 24 h period was reported.

Statistical analysis

Descriptive statistics are reported; counts, percentages and ages are presented for categorical data. Continuous data is reported by mean and median (IQR). Chi squared tests were performed for categorical variables. Kruskal-Wallis tests compared continuous variables between the crystalloid and PRBC group.

Risk adjustment was performed by creating a multivariate logistic regression model to predict both mortalities, utilising the covariates age, SBP, ISS, MOI. Adjusted Odds Ratios (OR) and Confidence Intervals (CI) are reported.

Statistical analysis was performed using R, version 3.4.0 [43]. Multiple imputation (MI) was employed to limit the effect of missing data in several covariates using the MICE package in R. Predictive mean matching was used, and ten data sets were imputed. Kernel density plots revealed a satisfactory imputation for ISS, MOI, massive transfusion, major transfusion and 28 d mortality.

Logistic regression models were constructed for all imputed datasets, and coefficients estimates pooled according to Rubin's rules [44]. Statistical significance was assumed as $p < 0.05$.

Ethical approval

This study met National Institute of Health Research (UK) criteria for Service Evaluation. Internal approval by KSSAAT Research Audit and Development Committee was gained. Formal ethical approval was not required. Patient identifiable data was anonymised and stored on electronic devices with technical encryption (Data Protection Act, 1998).

Results

During the study period, 218 patients met the inclusion criteria (Fig. 1). The crystalloid group comprised 109 patients, with 6 patients excluded for missing data ($n = 103$). The PRBC group comprised 109 patients, of which 17 patients were excluded for missing data ($n = 92$).

The reasons for exclusion comprised: 1) incomplete pre-hospital data, from patient clinical records, and 2) incomplete in-hospital data, from TARN and/or in-hospital electronic records. During the study period there were no immediate transfusion complications, and 100% traceability of pre-hospital PRBC was achieved.

Missing data in the crystalloid group was noted for 28 d mortality (26%); major transfusion (5%) and massive transfusion (5%). Missing data in the PRBC group is noted for 28 d mortality (15%); major transfusion (3%) and massive transfusion (3%). MI was therefore employed.

Demographics and incident descriptors

Patient demographics are reported (Table 1). Both groups were predominantly male ($p = 1.0$) and similar in age, mean 44 years ($p = 0.50$). Patient characteristics were comparable for SBP ($p = 0.56$) and ISS, 31 and 32, respectively ($p = 0.67$). Incident descriptors report no difference between the MOI in each group ($p = 0.73$).

Table 1 Categorical variables and covariates for the crystalloid and PRBC group; SBP, Systolic Blood Pressure; ISS, Injury Severity Score; MOI, Mechanism of Injury; RTC, Road Traffic Collision; IQR, Interquartile Range; N/A, Not Available

	Crystalloid Group	PRBC Group	*P* value
	n = 103	*n* = 92	
Gender			
Female (*n*, %)	26 (25)	24 (26)	
Male (*n*, %)	77 (74)	68 (73)	1.00
Age (mean, SD)	45 (20)	43 (20)	0.50
SBP (mean, SD)	88.21 (25)	90.65 (32)	0.56
ISS (mean, SD)	31.37 (14)	32.26 (12)	0.67
Median 999 time to HEMS on scene time (minutes, IQR)	30 (IQR 23.25–41.75)	35 (IQR 24–51.5)	
MOI (*n*, %)			
RTC Driver	17 (16)	18 (19)	0.73
RTC Passenger	10 (9)	11 (11)	
RTC Pedestrian	8 (7)	18 (19)	
RTC Motorcyclist	22 (21)	13 (14)	
Fall	10 (9)	9 (9)	
Penetrating Injury	2 (1)	5 (5)	
Pedal Cyclist	6 (5)	5 (5)	
Other	9 (8)	7 (7)	
N/A	19 (18)	6 (6)	
Mortality			
	6 h mortality		
No (*n*, %)	84 (81)	82 (89)	0.2
Yes (*n*, %)	19 (18)	10 (10)	
28 d mortality			
No (*n*, %)	45 (59)	57 (73)	0.09
Yes (*n*, %)	31 (40)	21 (26)	

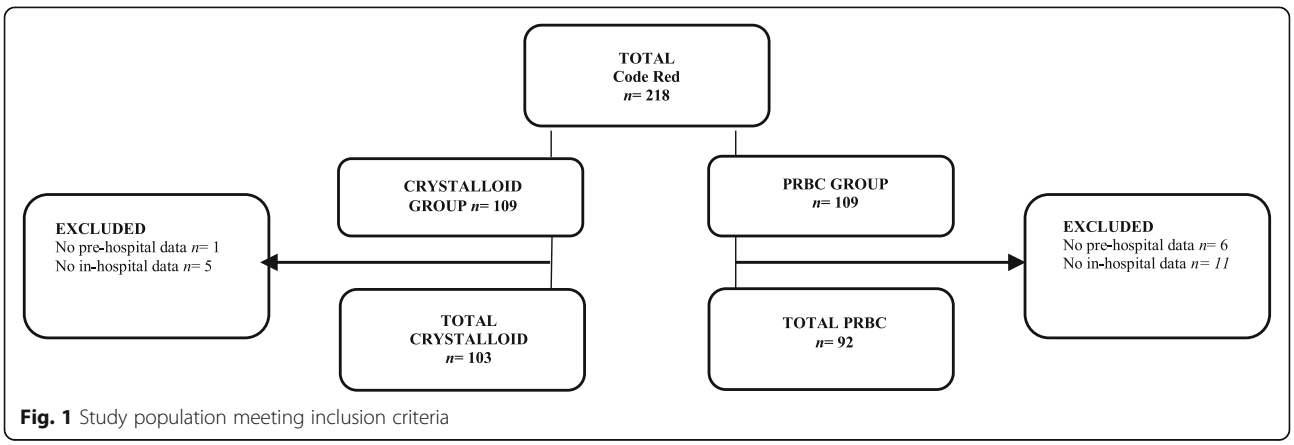

Fig. 1 Study population meeting inclusion criteria

In the crystalloid group, an average of 737 mL (IQR 250–1000 mL) of crystalloid was administered by HEMS, compared to 52 mL crystalloid and a median 2.3 PRBC units (IQR 1–3) in the PRBC group. The median PRBC received over the first in-hospital 24 h is documented for the crystalloid group as 4.5 units (IQR 2–9) and for the PRBC group as 3 units (IQR 1–8).

Primary outcome measure

Unadjusted analysis for observed 6 h mortality was less in the PRBC group ($n = 10$, 10%) versus the crystalloid group ($n = 19$, 18%) but not significantly so, $p = 0.2$. Similarly, for unadjusted 28 d mortality, there was an observed reduction in mortality in the PRBC group ($n = 21$, 26%) versus the crystalloid group ($n = 31$, 40%), $p = 0.09$. However, adjusted odds ratios (OR), after MI for both 6 h and 28 d mortality show no statistically significant association (Table 2).

Massive and major transfusion sub-analysis

Observed frequencies report a statistically significant, greater proportion, of the crystalloid group requiring a major transfusion ($n = 62$, 60% versus, $n = 41$, 40%), $p = 0.02$. There was no statistical difference in the proportion of the crystalloid group requiring a massive transfusion ($n = 22$, 22%) compared to the PRBC group ($n = 14$, 15%), $p = 0.31$.

Adjusted odds ratios, after MI, show no statistically significant association for major transfusion in 6 h mortality ($p = 0.11$) and 28 d mortality ($p = 0.22$). For massive transfusion, there is no statistically significant association for massive transfusion in 6 h mortality ($p = 0.11$). For massive transfusion, there is a non-statistically significant association for transfusion of PRBC and 28 d mortality ($p = 0.07$) (Table 3).

Discussion

Observed mortality rates are less in the PRBC group at 6 h and 28 days, but not significantly so. Equally, mortality of patients in the major and massive transfusion sub-analysis shows an observed reduction, but not significantly so. Patients receiving pre-hospital PRBC were significantly less likely to receive a major transfusion. To our knowledge this is the first UK HEMS paper to report on patient outcomes following the introduction of pre-hospital PRBC transfusion.

Table 2 Odds ratios for 6 h and 28 d mortality (after multiple imputation adjusted for age, ISS, SBP, MOI)

Mortality	OR	Lower 95% CI	Upper 95% CI	*P* value
6 h	0.48	0.19	1.19	0.11
28 d	0.66	0.32	1.35	0.26

Table 3 Odds ratios for 6 h and 28 d mortality in the massive transfusion and major transfusion (after multiple imputation adjusted for age, ISS, SBP, MOI)

	OR	Lower 95% CI	Upper 95% CI	*P*- value
Major Transfusion				
6 h mortality	0.35	0.10	1.27	0.11
28 d mortality	0.55	0.21	1.43	0.22
Massive Transfusion				
6 h mortality	0.04	0.00	2.10	0.11
28 d mortality	0.02	0.00	1.48	0.07

Patient demographics in our study were consistent with published literature. A large proportion of the patients were male [29, 31, 45] with a mean age of 44 years [29, 31, 45]. The ISS of 31 (crystalloid group) and 32 (PRBC group) is close to the mean ISS of 27.5 reported in a systematic review [2] and other studies on pre-hospital fluid resuscitation [32, 45], confirming that substantial anatomical injuries are present in patients with traumatic haemorrhage [2].

Incident descriptors in this study are consistent with the published literature, with a high proportion of blunt traumatic injuries [31]. Median pre-hospital PRBC transfusion comprised 2 units; similar to other UK data [45], consistent with HEMS clinicians focusing on a short scene time to deliver a package of care derived from damage control resuscitation techniques. Overall mortality is approaching 40% for the crystalloid group, consistent with published literature [2], and 27% for the PRBC group.

There was an observed reduction in the crude frequency for mortality at 6 h in the PRBC group, however, adjusted OR after MI was not statistically significant ($p = 0.11$). Other studies have demonstrated no statistically significant difference in 6 h mortality [8]. Early deaths are likely due to exsanguination; requiring future innovation early in the critical window [14]. In the absence of other pre-hospital homeostatic interventions, transfusing large volumes of blood product pre-hospital [45] may 'bridge the gap' to definite haemorrhagic control. Equally, in future studies, blood product transfusion in addition to such techniques may well provide survival benefit [45].

There was an observed reduction in the crude frequency for mortality at 28 d in the PRBC group, however, adjusted OR after MI was not statistically significant ($p = 0.26$). One systematic review of 27 observational studies suggests no overall statistically significant survival benefit; however, the review evidences improved survival at 24 h [38]. Other small single centre pilot studies found no difference in 24 h (OR 0.57, $p = 0.12$) or 30 d mortality (OR 0.71, $p = 0.44$), despite improved early outcomes. Group characteristics and mode of transport make group comparability difficult. Other studies have revealed no survival benefit [6, 46]. We

hypothesise that the number of patients in our study resulted in insufficient power to detect a true difference. As reported by Smith et al. (28), review of 'grey' low quality evidence with small patient populations may hide any survival benefit.

Interestingly we note a reduction in 6 h mortality in the major transfusion and massive transfusion subgroup ($p = 0.11$). In the massive transfusion subgroup 28 d mortality shows mild evidence for improved survival ($p = 0.07$). Arguably at 28 days, death is not due to exsanguination alone; instead coagulopathy, inflammation, immunosuppression and MODS are intrinsically linked [14]. It is plausible that early PRBC transfusion in the immediate resuscitation phase mitigates elements of the post-traumatic coagulopathy by avoiding the haemodilution of erythrocytes with oxygen carrying capability noted in aggressive crystalloid resuscitation [14].

In recent literature the mortality rate for patients with a major haemorrhage approached 50%, this evidence has a similar proportion of patients requiring a massive transfusion to those in our study [14]. It was discussed that during the critical window, blood component therapy was below recommended thresholds, thus, haemostatic competence was not maintained. This may also be one explanation for our observed values.

Brown's multicentre prospective cohort study (2015) found an independent association between PRBC and the reduction in risk of mortality in a civilian population. Of 1415 patients, 50 received PRBC transfusion and were matched to a cohort of 113 subjects [6]. Propensity score matching documented 98% reduction in odds of 24 h mortality ($p = 0.04$), and 88% reduction in the risk of 30 d mortality ($p = 0.01$). However, raw mortality was not reported, nor were variables used in multivariate regression analysis. In addition, overall mortality for patients requiring a pre-hospital transfusion is reported as 4%, inconsistent with, and considerably lower than, our study and other literature [2]. Notably, half of the transfused patients were inter-hospital transfusions introducing survival bias and reducing external validity in comparison to a primary HEMS cohort of patients.

Conversely, the Pre-hospital Resuscitation on Helicopter Study (PROHS) group reported a multicentre prospective observational study of pre-hospital transfusion in civilian patients [35]. Propensity score matching of 109 patients identified no significant difference between pre-hospital transfusions in a PRBC and plasma group, compared to crystalloid for mortality at 3 h, 24 h and 30 d [35]. Of these patients, 24% received plasma only and 7% PRBC only. Coupled with unexpected differences in SBP, GCS and ISS, only 10% of patients could be matched leading to inconclusive results.

Early haemorrhagic death comprises a notable proportion of patients who may benefit from early transfusion; therefore, including these deaths is critical [47]. By adopting a conditional 30-day survival analysis among 24 h survivors, studies have introduced a survival bias by excluding early haemorrhagic deaths [47, 48]. Rehn et al. (2018) report increased survival to hospital in a before and after study of pre-hospital PRBC transfusion [45]. The 'delayed death' concept would result in a larger proportion of patients surviving to hospital, but then going on to die shortly after, resulting in the observed mortality at 6 h shown in our study. This concept provides impetus to advancing in-hospital strategies to improve survival [45].

There was a significant difference between the frequency of patients receiving a major transfusion in the crystalloid (63%) versus PRBC group (46%), $p = 0.02$. This is consistent with previous work [45]. Critically, this likely reflects advancing in-hospital major haemorrhage protocols. The authors are aware that stratification on post-treatment surrogates for injury severity (massive transfusion, ISS) introduces bias [47]. For example, even an international multi-centre retrospective analysis of over 3000 patients could not define a threshold at which massive transfusion equals poorer outcomes [5]. However, in the absence of other measures, massive and major transfusion was used here to retrospectively identify haemorrhagic patients [49]. Arguably, there is no universal approach to massive transfusion; hence, emerging evidence for the clinical application of TEG and ROTEM to detect ATC [49].

Study limitations

Methodological limitations are inherent within an observational retrospective study. The results of any post hoc design is to be appraised with caution, due to inherent confounding and uncontrolled bias. Although there were no pre-hospital system alterations during the study period other than the resuscitation fluid, there is a natural assumption of unaccounted, uncontrolled change and general improvement to resuscitation care and clinical practice. By excluding the PRBC introduction and implementation phase, variability in clinical practice could have been limited during this study period [45].

The authors are cognisant that this paper crosses a study period where, by virtue of time, there were considerable in-hospital advances. Major Trauma Networks, including MTCs were introduced across London during 2010 and extended throughout in the UK in 2012 which would have enabled wide clinical benefit for patients requiring time critical intervention. More specifically, massive transfusion protocols have moved away from managing a late dilutional coagulopathy. Historically in-hospital transfusion protocol managed the result of large volume crystalloid and PRBC transfusion [14]. To illustrate this, in one UK MTC, mortality reduced from 50 to 26% over a 6-year period and transfusion of blood

product halved [14]. Local variation in major transfusion protocols confounds comparisons between each MTC.

Similarly, advances in pre-hospital ambulance practice, such as: technical skills around appreciation of clot preservation, pelvic binding, prioritisation of TXA administration and intra-osseous access have developed [50]. The CRASH-2 trial has shown that administration of TXA to bleeding trauma patients who are within 3 h of injury, significantly reduces all-cause mortality and death due to bleeding (risk ratio (RR) = 0.72, 95% CI 0.63, 0.83). Other potential confounders such as body temperature and pre-hospital anaesthetic agents/co-medications are not reported.

Loss to follow up, and incomplete patient records from both the pre-hospital and in-hospital phases, produced substantial missing data. Notably, 26% of follow up data is missing in the crystalloid group. To address this, MI of 10 datasets was employed [39, 44, 51]. However, it is likely that the incidence of Code Red patients in the region is slightly underestimated; due to incident proximity some patients will be transferred directly to an MTC by land ambulance, without HEMS input. In addition, if the transit time was short, patients seen by HEMS may trigger a massive transfusion on arrival at hospital, with no time to perform pre-hospital transfusion, therefore effectively removing the patient from the inclusion criteria used in this study. This study would be strengthened if the approximate point of injury (999 time) had been recorded in relation to the transfusion of PRBC, and total pre-hospital time, as opposed to the 'on scene' surrogate given.

A case can be argued for following the intensive care principle of 'critical care without walls'; treating the Code Red patient on the basis of clinical need and not geographical location [52]. Future comparison studies are likely complicated by the administration of different types and quantity of blood product across services (e.g. Fibrinogen, FFP, FDP), however, collaborative prospective research amongst UK HEMS will provide larger sample sizes and generate further discussion. It may be more important that future work targets precision resuscitation in the coagulopathic patient. Improved diagnostics and therapeutics at the scene as adjuncts to current strategies are warranted, enabling focused delivery of blood products at the point of injury.

Conclusion

In a single centre, retrospective UK HEMS study, observed mortality at 6 h and 28 days is reduced in a group of patients with suspected traumatic haemorrhage who received a PRBC transfusion compared to crystalloid. This is also reflected in a massive transfusion subgroup; however, both are statistically non-significant. Patients receiving pre-hospital PRBC were significantly less likely to need an in-hospital major transfusion compared to those receiving pre-hospital crystalloid. Further multi-centre prospective research, with adequate power to detect a true difference in patient survival, is required to establish the optimum strategy for pre-hospital volume replacement in patients with traumatic haemorrhage.

Abbreviations

ATC: Acute Trauma Coagulopathy; CI: Confidence Interval; FDP: Freeze dried plasma; FFP: Fresh frozen plasma; GCS: Glasgow Coma Score; HEMS: Helicopter Emergency Medical Services; IQR: Interquartile Range; ISS: Injury Severity Score; KSSAAT: Kent, Surrey & Sussex Air Ambulance Trust; MI: Multiple Imputation; MODS: Multiple organ dysfunction; MOI: Mechanism of injury; MTC: Major Trauma Centre; NIHR: National Institute for Health Research; OR: Odds Ratio; PRBC: Packed red blood cells; ROSC: Return of spontaneous circulation; ROTEM: Rotational Thromboelastometry; SBP: Systolic blood pressure; SD: Standard deviation; TARN: Trauma Audit Research Network; TEG: Thromboelastography; TIC: Trauma Induced Coagulopathy

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JG, JJ and RL were involved in study design. JG, SD and EDS performed data collection. MJ performed statistical analysis. Data analysis was reviewed by all authors. All authors involved in manuscript preparation and submission. All authors read and approved the final manuscript.

Ethics approval and consent to participate

National Institute of Health Research criteria for Service Evaluation was met. Internal approval by KSSAAT Research Audit and Development Committee was gained. Formal ethical approval was not required. Patient identifiable data was anonymised and stored on electronic devices with technical encryption (Data Protection Act, 1998).

Consent for publication

Not applicable.

Competing interests

JG, JJ, RL, MQR, ND, SD, DB and GW are all employees of Kent, Surrey and Sussex Air Ambulance Trust. There were no other financial or non-financial conflicts of interest.

Publisher's Note

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Performance of the CURB-65 Score in Predicting Critical Care Interventions in Patients Admitted With Community-Acquired Pneumonia

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Study objective: Confusion, uremia, elevated respiratory rate, hypotension, and aged 65 years or older (CURB-65) is a clinical prediction rule intended to stratify patients with pneumonia by expected mortality. We assess the predictive performance of CURB-65 for the proximal endpoint of receipt of critical care intervention in emergency department (ED) patients admitted with community-acquired pneumonia.

Methods: We performed a retrospective analysis of electronic health records from a single tertiary center for ED patients admitted as inpatients with a primary diagnosis of pneumonia from 2010 to 2014. Patients with a history of malignancy, tuberculosis, bronchiectasis, HIV, or readmission within 14 days were excluded. We assessed the predictive accuracy of CURB-65 for receipt of critical care interventions (ie, vasopressors, large-volume intravenous fluids, invasive catheters, assisted ventilation, insulin infusions, or renal replacement therapy) and inhospital mortality. Logistic regression was performed to assess the increase in odds of critical care intervention or inhospital mortality by increasing CURB-65 score.

Results: There were 2,322 patients admitted with community-acquired pneumonia in the study cohort; 630 (27.1%) were admitted to the ICU within 48 hours of ED triage and 343 (14.8%) received a critical care intervention. Of patients with a CURB-65 score of 0 to 1, 181 (15.6%) were admitted to the ICU, 74 (6.4%) received a critical care intervention, and 7 (0.6%) died. Of patients with a CURB-65 score of 2, 223 (27.0%) were admitted to the ICU, 127 (15.4%) received a critical care intervention, and 47 (5.7%) died. Among patients with CURB-65 score greater than or equal to 3, 226 (67.0%) were admitted to the ICU, 142 (42.1%) received a critical care intervention, and 43 (12.8%) died. The areas under the receiver operating characteristic for CURB-65 as a predictor of critical care intervention and mortality were 0.73 and 0.77, whereas sensitivity of CURB-65 score greater than or equal to 2 in predicting critical care intervention was 78.4%; for mortality, 92.8%.

Conclusion: Patients with CURB-65 score less than or equal to 2 were often admitted to the ICU and received critical care interventions. Given this finding and the relatively low sensitivity of CURB-65 for critical care intervention, clinicians should exercise caution when using CURB-65 to guide disposition. Future ED-based clinical prediction rules may benefit from calibration to proximal endpoints. [Ann Emerg Med. 2018;■:1-9.]

Please see page XX for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background and Importance

Pneumonia is a leading cause of emergency department (ED) visits and hospital admissions.[1] Critical to the management of patients with pneumonia is initial disposition: whether to provide care in the outpatient setting, admit to the hospital ward, or admit to the ICU. To address this management decision, the Infectious Diseases Society of America/American Thoracic Society consensus guidelines and British Thoracic Society guidelines recommend incorporating clinical prediction rules into clinical decisionmaking alongside physician judgment.[2,3]

One such proposed prediction rule, the confusion, uremia, elevated respiratory rate, hypotension, and aged 65 years or older (CURB-65) score, was derived to estimate 30-day mortality in patients with community-acquired pneumonia. The score was derived and validated from approximately 1,000 patients admitted to the hospital with community-acquired pneumonia and was found to effectively stratify patients by increasing risk of 30-day mortality.[4] On the basis of a low predicted mortality, the authors of the original article suggested that patients with a CURB-65 score of 0 to 1 (mortality <2%) may be suitable for outpatient management and those with a score of 2 may

Editor's Capsule Summary

What is already known on this topic

Confusion, uremia, elevated respiratory rate, hypotension, and aged 65 years or older (CURB-65) predicts 30-day mortality in patients with community-acquired pneumonia and is recommended as an aid to disposition decisions.

What question this study addressed

How frequently do patients classified as being at low risk for mortality by CURB-65 require critical care interventions in the course of their illness?

What this study adds to our knowledge

Two thousand two hundred thirty-two eligible inpatients with community-acquired pneumonia were retrospectively identified. Of 480 patients in the lowest CURB-65 risk category, few died (0.6%) but 4.2% received vasopressors, assisted ventilation, invasive catheters, an insulin drip, or dialysis.

How this is relevant to clinical practice

Although somewhat useful in predicting mortality, CURB-65 does not appear to make clinically useful predictions about the level of inpatient care a patient will require.

be suitable for ward-level care or observation.[4] These suggestions have made their way into clinical practice, in which electronic incorporation of the score has been recommended to be used as a real-time decision support tool.[5,6] In our local observations, CURB-65 has been included electronically in the ED interface, and is often cited in discussions between ED clinicians and admitting teams in regard to disposition decisions.

The calibration of prediction rules to mortality in admitted patients, however, fails to account for the potential benefit of interventions received by patients while hospitalized. These interventions may be in the pathway of survival or nonsurvival and therefore should be considered when disposition decisions are made. A young patient without significant comorbidities who presents with severe pneumonia, for example, may require a period of assisted ventilation but is likely to survive. The more proximal "need for critical care intervention" (or even elements of hospital care such as supplemental oxygen, vital signs monitoring, and intravenous antibiotics) may be more pertinent to the front-line provider than whether the patient ultimately lives or dies. As has been recently noted, the field of clinical prediction in pneumonia should move on from the endpoint of mortality and instead focus on proximal outcomes with more relevance to decisionmaking.[7] The relationship between the CURB-65 score and need for critical care intervention has yet to be comprehensively studied.

Goals of This Investigation

We performed a retrospective validation study of the CURB-65 prediction instrument on our own patient population, adding several transitional outcomes not addressed in previous studies. Specifically, we assessed the predictive performance of the CURB-65 score in patients with community-acquired pneumonia with respect to the proximal endpoint of critical care intervention. We further aimed to determine how frequently patients with a low predicted risk of mortality by CURB-65 score receive critical care interventions early in their hospital stay.

MATERIALS AND METHODS

Study Design and Selection of Participants

This was a single-center, retrospective study conducted at an urban tertiary care center with approximately 57,000 ED visits annually. Patients presenting to the ED between January 2010 and December 2014 with suspected infection and who were admitted to the hospital as inpatients with a primary admission diagnosis of pneumonia (as determined by the admitting emergency physician) were included in the study. The period was selected because our database was constructed with *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes for certain variables. Our selection criteria were guided by the criteria for eligibility used in the original CURB-65 derivation study; thus, patients readmitted within 14 days, as well as those with a history of malignancy, tuberculosis, bronchiectasis, or HIV (as determined by *ICD-9* code), were excluded. The institutional review board at Beth Israel Deaconess Medical Center approved this study.

Data Collection and Processing

The electronic medical records for each included patient were queried, and demographic data, vital signs, and laboratory results were abstracted. Vital signs considered outside of the physiologic range were interpreted as chart documentation errors and were considered missing (ie, pulse rate <30 or ≥ 200 beats/min, respiratory rate <4 or ≥ 60 breaths/min, and systolic blood pressure <50 or ≥ 250 mm Hg). For all patients with missing vital signs, manual chart review was performed to extract vital signs. Medical comorbidities were determined with previously established *ICD-9* codes for various conditions.[8]

For calculation of the CURB-65 score, the worst values for each criterion measured in the ED (for blood pressure) or in the first 24 hours after ED triage (for laboratory values) were used.

An *ICD-9* code suggesting altered mentation (780.0, 780.09, 780.02, 780.97, 349.82, and 348.31) documented by an ED clinician or a documented ED chief complaint suggesting altered mentation (eg, altered mental status, confusion, change in mental status) was used to determine whether an alteration in mental status was present. This methodology has been previously applied to determine mental status.[9]

Outcome Measures

The primary outcome of this study was "received critical care intervention" within 48 hours of ED triage. Interventions classified as critical care interventions were determined by review of the literature[10-12] and as used in a previous study.[9] Critical care interventions included receipt of vasopressor or ionotropic support agents (norepinephrine, phenylephrine, vasopressin, epinephrine, dopamine, dobutamine, and milrinone), receipt of assisted ventilation (either invasive or noninvasive), receipt of a continuous insulin infusion, receipt of greater than 4,000 mL of intravenous fluid within 12 hours of ICU admission, placement of invasive catheters (central venous line, pulmonary artery catheter, arterial line, or balloon pump), or renal replacement therapy (Figure 1). Critical care interventions were determined with structured data from our high-resolution ICU database. Patients initially admitted to a ward level of care but subsequently transferred to an ICU and provided a critical care intervention within 48 hours of ED triage were categorized as having received a critical care intervention. Therefore, any critical care intervention was included regardless of initial physician choice of admission location. Information in regard to inhospital mortality was also abstracted from the electronic medical record.

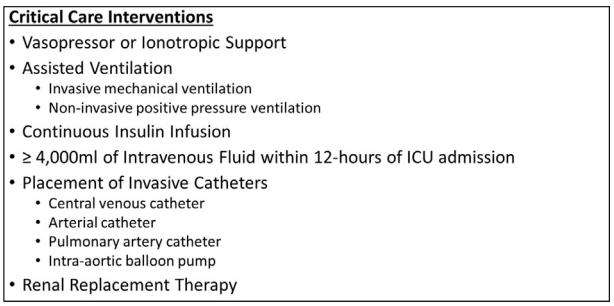

Figure 1. Critical care interventions.

Primary Data Analysis

Descriptive data are presented as means with SD or medians with interquartile ranges, depending on the distribution of the data. Categorical data are presented as counts with relative frequencies. Between-group comparisons were made with χ^2 tests for categorical data and 2-sample t tests or Wilcoxon rank sum tests for continuous data as appropriate. Standard normal values were imputed for missing values, as has been done in other studies exploring prognostic scores.[13] Overall, data loss was very low for all CURB-65 variables (<1%).

Model discrimination was determined on the basis of the area under the receiver operating characteristic (AUROC). Sensitivities and specificities were calculated at a cutoff of CURB-65 score greater than or equal to 2, as has been previously suggested.[2,3] CURB-65 test characteristics were also explored at other cutoff points. Logistic regression was used to assess the stepwise increase in odds of receiving a critical care intervention or experiencing inhospital mortality by increasing CURB-65 score. To compare stepwise mortality in our cohort with that of the CURB-65 derivation cohort, we created a new data set using data from the original CURB-65 study that included the number of patients in the cohort with each CURB-65 score and the number of patients with each CURB-65 score who died. Logistic regression was used in the new data set to assess the stepwise increase in odds of mortality with increasing CURB-65 score.

A 2-tailed $P<.05$ was considered statistically significant. All statistics were performed with Stata (version 14; StataCorp, College Station, TX).

RESULTS

Characteristics of Study Subjects

A total of 24,164 patients presented to the ED and were admitted to the hospital with suspected infection during the study period. Of these, 2,322 patients (9.6%) were admitted with a primary diagnosis of community-acquired pneumonia. The mean age of patients admitted with pneumonia was 69.0 years (SD 17.6 years) and 50.0% were women. For complete characteristics of the study cohort, see Table 1. There were 489 patients (21.1%) who were initially admitted to the ICU and 1,833 (78.9%) initially admitted to a ward level of care (Figure 2).

Of the 2,322 patients in the cohort, 1,159 (49.9%) had a CURB-65 score of 0 to 1, 826 (35.6%) had a score of 2, and 337 (14.5%) had a score greater than or equal to 3. For a complete breakdown of score distribution, see Table 2.

Of the 1,833 patients initially admitted to a ward level of care, 1,040 (56.7%) had a CURB-65 score of 0 to 1, whereas 793 (43.3%) had a score greater than or equal to 2.

Table 1. Baseline characteristics.

Characteristics	All Patients (n=2,322)	Received Critical Care Intervention (n=343)	No Critical Care Intervention (n=1,979)
Demographics			
Mean age (SD), y	69.0 (17.6)	68.8 (17.6)	69.0 (17.6)
Women, No. (%)	1,162 (50.0)	151 (44.0)	1,011 (51.1)
Vital signs, mean (SD)			
Systolic blood pressure, mm Hg	120.7 (24.1)	106.8 (26.2)	123.2 (23.8)
Respiratory rate, breaths/min	22.6 (6.2)	26.7 (7.7)	21.9 (5.6)
Temperature, °F, °C	99.5 (1.8), 37.5 (0.68)	99.5 (2.0), 37.5 (0.68)	99.5 (1.7), 37.5 (0.68)
Pulse rate, beats/min	97.8 (20.5)	105.0 (23.6)	96.5 (19.7)
Mental status			
AMS, No. (%)	153 (6.7)	32 (9.3)	124 (6.3)
Laboratory measurements, median (IQR)			
WBC count, K/uL	11.3 (8.0–15.4)	13.4 (9.6–18.0)	11.0 (7.8–14.8)
BUN, mg/dL	21.0 (14.0–31.0)	31.0 (20.0–50.0)	19.0 (14.0–29.0)
Lactate, mmol/L	1.6 (1.3–2.2)	2.2 (1.6–3.3)	1.5 (1.3–2.0)
Comorbidities, No. (%)			
CHF	624 (26.8)	142 (41.4)	482 (24.4)
Renal disease	551 (23.7)	94 (27.4)	457 (23.1)
Liver disease	131 (5.6)	25 (7.3)	106 (5.4)
Diabetes	661 (28.5)	118 (34.7)	542 (27.4)

AMS, Altered mental status; *IQR*, interquartile range; *BUN*, blood urea nitrogen; *CHF*, congestive heart failure.

Of the 489 patients initially admitted to the ICU, 119 (24.3%) had a CURB-65 score of 0 to 1, 174 (35.6%) had a score of 2, and 196 (40.1%) had a score greater than or equal to 3.

There were 141 patients (6.1%) initially admitted to a ward level of care who were transferred to the ICU within 48 hours of ED triage. Among these patients, 62 (44.0%) had a CURB-65 score of 0 to 1 and 49 (30.5%) had a score of 2. Overall, 181 patients (15.6%) with a score of 0 to 1 and 223 (27.0%) with a score of 2 were admitted to the ICU within 48 hours. See Figure 2 for the patient flow diagram. Higher CURB-65 score was a predictor of need for ICU transfer for patients initially admitted to the floor (odds ratio [OR] 1.6; 95% confidence interval [CI] 1.4 to 2.0).

Including ward transfers, there were 630 patients admitted to the ICU within 48 hours of ED triage, and 343 (54.4%) of these patients received at least one critical care intervention. Of patients with a CURB-65 score of 0 to 1, 74 (6.4%) received a critical care intervention compared with 127 (15.4%) patients with a score of 2 and 142 (42.1%) with a score greater than or equal to 3. For a complete distribution of critical care interventions received by CURB-65 score, see Table 2.

Compared with patients with a CURB-65 score of 0 to 1, those with a score of 2 (OR 2.7; 95% CI 2.0 to 3.6; $P<.001$) and those with a score of 3 to 5 (OR 10.7; 95% CI 7.8 to 14.7; $P<.001$) were more likely to receive critical care interventions. Among patients receiving critical care interventions, central venous line (n=200; 61.9%), intubation (n=169; 49.3%), and vasopressor administration (n=144; 42.0%) were the most common.

Of patients with a CURB-65 score of 0 to 1 who were admitted to the ICU, 36 (19.9%) underwent intubation and 14 (7.7%) received noninvasive positive-pressure ventilation but were not intubated. See Table 2 for rates of all critical care interventions by score.

Overall, 97 patients (4.2%) died inhospital. Among patients with CURB-65 score 0 to 1, 7 (0.6%) died compared with 90 (7.7%) with a score greater than or equal to 2. We found that there was a stepwise increase in mortality for each increase in the CURB-65 score, with lower levels of mortality than those in the original study (Figure 3). Specifically, when the cohort was split into groups based on CURB-65 scores 0 to 1, 2, and 3 to 5, there was a stepwise increase in mortality by increasing score in both the original CURB-65 derivation study[4] and in the present study cohort. Compared with patients with a CURB-65 score of 0 to 1, patients in the present study cohort with a score of 2 (OR 9.9; 95% CI 4.5 to 22.1) and those with a score of 3 to 5 (OR 24.1; 95% CI 10.7 to

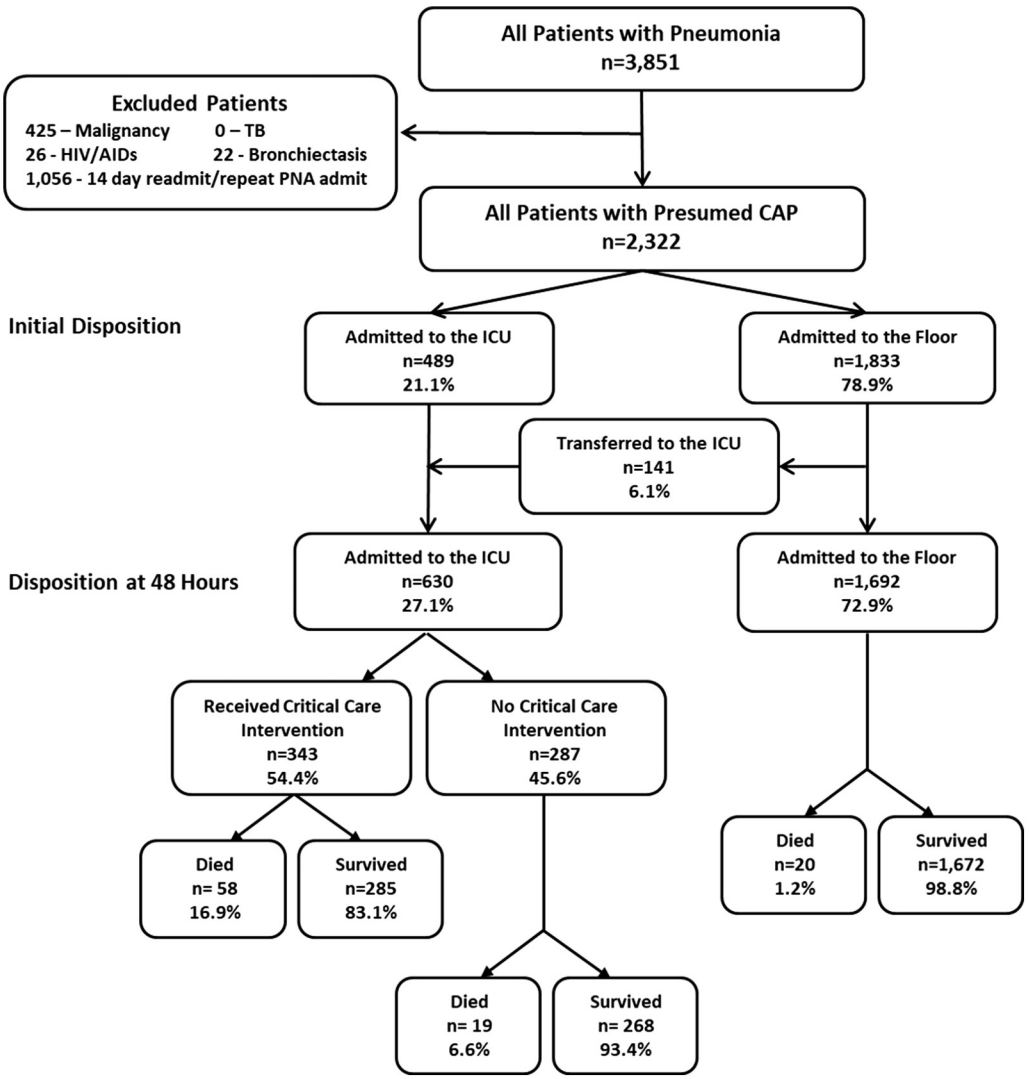

Figure 2. Disposition of patients admitted with pneumonia. *PNA*, Pneumonia; *CAP*, commonly acquired pneumonia.

54.1) were more likely to experience inhospital mortality. In the original study cohort, patients with a CURB-65 score of 2 (OR 6.5; 95% CI 2.4 to 17.9) and 3 to 5 (OR 18.4; 95% CI 7.2 to 47.2) had a higher likelihood of 30-day mortality compared with those with a score of 0 to 1. For a detailed distribution of critical care intervention and mortality by CURB-65 score, see Figure 3.

The AUROC for CURB-65 score was 0.73 (95% CI 0.71 to 0.76) (Figure 4) for critical care intervention and 0.77 (95% CI 0.73 to 0.81) for mortality. The sensitivity of CURB-65 score greater than or equal to 2 in predicting critical care intervention was 78.4% (95% CI 73.7% to 82.7%) and was lower than that for mortality, at 92.8% (95% CI 85.7% to 97.0%), whereas the specificity was low for both outcomes, at 54.8% (95% CI 52.6% to 57.0%) and 51.8% (95% CI 49.7% to 53.9%), respectively, when a cut point of greater than or equal to 2 was chosen. See Table 3 for CURB-65 test characteristics at additional cut points.

LIMITATIONS

Our study is subject to a number of limitations. Similar to the original CURB-65 derivation,[4] the study was conducted at a tertiary care center in an urban setting, thereby limiting the generalizability of the results. In particular, because it is a tertiary care referral center, many patients presenting with pneumonia have multiple medical comorbidities, which may increase the apparent clinical severity of patients with low CURB-65 scores. Related to this, we estimate that less than 10% of patients presenting to our ED with pneumonia are discharged home. As in the original CURB-65 derivation study, our cohort included only patients admitted to the hospital after presenting with pneumonia and excluded those who were being readmitted

Table 2. Critical care interventions and mortality by CURB-65 score.

	CURB-65 Score (n=2,322)					
Outcome	**0 (n=480)**	**1 (n=679)**	**2 (n=826)**	**3 (n=267)**	**4 (n=67)**	**5 (n=3)**
ICU intervention, % (95% CI)						
Any	4.2 (2.6–6.4)	8.0 (6.0–10.2)	15.4 (13.0–18.0)	35.6 (29.8–41.7)	67.2 (54.6–78.2)	66.7 (9.4–99.2)
Vasopressor	0.4 (0.0–1.5)	1.9 (1.0–3.3)	5.6 (4.1–7.4)	19.1 (14.6–24.3)	46.3 (34.0–58.9)	33.3 (0.8–90.6)
IPPV	1.9 (0.8–3.5)	4.0 (2.6–5.7)	6.7 (5.0–8.6)	17.2 (12.9–22.3)	44.8 (32.6–57.4)	66.7 (9.4–99.2)
NIPPV	1.7 (0.7–3.3)	1.3 (0.6–2.5)	4.5 (3.2–6.1)	8.2 (6.4–11.6)	6.0 (3.6–14.9)	0
Insulin gtt	0.2 (<0.1–1.1)	0.9 (0.3–1.9)	0.7 (0.2–1.6)	1.12 (0.2–3.2)	0	0
Invasive catheter	1.9 (0.9–3.5)	4.4 (3.0–6.3)	11.0 (9.0–13.4)	26.6 (21.4–32.3)	56.7 (44.0–68.8)	33.3 (0.8–90.6)
>4 L IVF	0.6 (0.1–1.8)	2.2 (1.2–3.6)	1.5 (0.7–2.4)	5.2 (2.8–8.6)	10.5 (4.3–20.3)	33.3 (0.8–90.6)
RRT	1.0 (0.3–2.4)	2.5 (1.5–4.0)	1.6 (0.8–2.7)	1.1 (0.2–3.2)	0	0
Mortality, % (95% CI)						
All	0.6 (0.1–1.8)	0.6 (0.1–1.5)	5.7 (4.2–7.5)	12.0 (8.3–16.5)	14.9 (7.4–25.7)	33.3 (0.8–90.6)
Admitted to floor (n=1,692)	0.5 (<0.1–1.7)	0.2 (<0.1–1.0)	2.0 (1.0–3.5)	2.9 (0.6–8.4)	12.5 (0.3–52.7)	100.0
Admitted to ICU (n=630)	2.0 (<0.1–10.6)	2.3 (0.4–6.6)	15.7 (11.1–21.1)	17.6 (12.1–24.3)	15.3 (7.2–27.0)	0

IPPV, Invasive positive pressure ventilation; *NIPPV*, noninvasive positive-pressure ventilation; *gtt*, continuous infusion; *IVF*, intravenous fluid; *RRT*, renal replacement therapy.

within 14 days and those with a history of malignancy, HIV, bronchiectasis, or tuberculosis. However, because of limitations of the available data, we were unable to exclude patients presenting from a nursing facility, as was done in the original study. Given that nursing home patients may represent a cohort with more compromised immune systems and different microbacterial exposures, our findings may be distorted if they were included in substantial numbers in our population. Nevertheless, we would expect the overall patterns of the findings (ie, that patients with CURB-65 scores 0 to 2 not infrequently receive critical care interventions despite very low mortality) to be unchanged. Additionally, it is possible that we were unable to identify patients recently admitted to other health care facilities. Although inhospital mortality was not the central focus of our investigation, we used it, whereas the original study used 30-day mortality as their primary endpoint.

In this study, we measured specific critical care interventions but did not include other aspects of ICU management such as close monitoring and high nurse-to-patient ratio. Furthermore, given the retrospective nature of the work, we were limited by available data and used unstructured ED data in addition to *ICD-9* codes in calculating the CURB-65 score. Although most follow-up investigation in regard to the CURB-65 score has relied on retrospective review using electronic medical records and administrative codes, this methodology may result in a decreased sensitivity for certain comorbidities.

The decision to perform a critical care intervention may be based on a combination of factors, some of which relate to the patient's clinical condition (eg, physiologic changes) and others that relate to the practice environment (eg, physician training, unit staffing). Nevertheless, we believe the decision to perform a critical care intervention compared with other outcome measures (eg, ICU admission) is more reflective of patient need as opposed to external factors. To this end, we have additionally captured critical care interventions received by patients initially admitted to the floor and then transferred to the ICU. Still, there is likely some residual subjectivity in the outcome of critical care intervention.

DISCUSSION

In this study, we assessed the predictive performance of the CURB-65 score, but used critical care interventions as

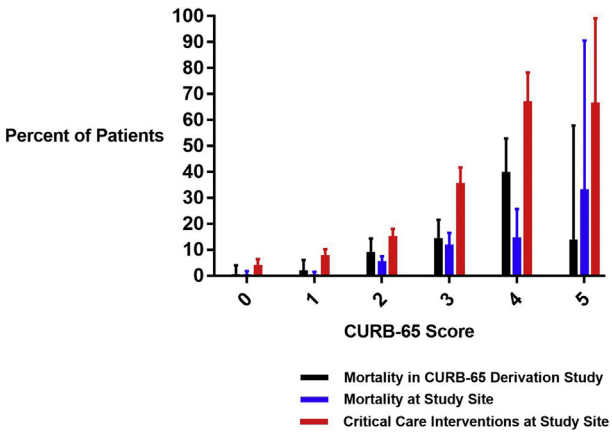

Figure 3. Mortality and critical care intervention rate by CURB-65 score.

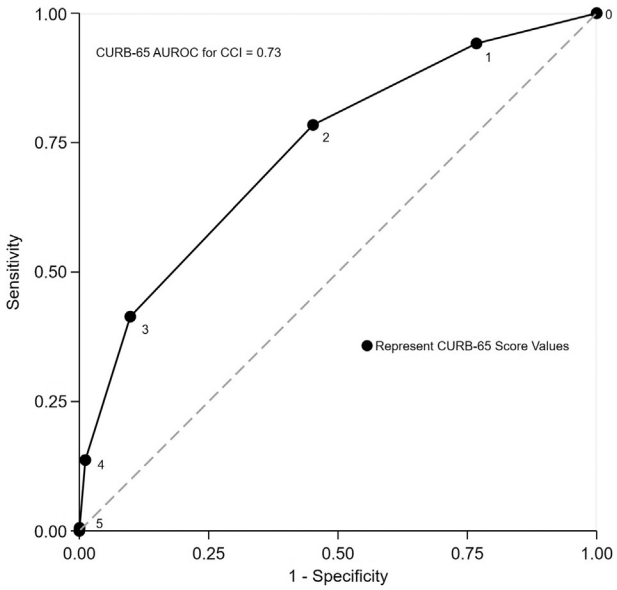

Figure 4. AUROC for CURB-65 in predicting critical care intervention.

our primary outcome of interest as opposed to 30-day mortality. In our study cohort, we found a stepwise increase in rates of critical care intervention and mortality for each point increase in the CURB-65 score. For patients with CURB-65 scores of 0 to 1, overall mortality was low (0.6%), as previously shown; however, many of these patients required ICU admission and received a critical care intervention. For example, 19.3% of patients with a CURB-65 score of 1 were admitted to the ICU and 8.0% received a critical care intervention. Among patients with a CURB-65 score of 2, for whom a short inpatient stay or closely supervised outpatient treatment has been suggested, 1 of every 6 received a critical care intervention. Thus, our overall findings suggest that patients with CURB-65 scores of 0 to 2 have a significant likelihood of receiving a critical care intervention despite low mortality rates.

The CURB-65 score was initially derived through the application of multiple logistic regression with an outcome of 30-day mortality to a population of 1,068 patients who presented to the ED and were admitted to the hospital with pneumonia. Since publication, the use of CURB-65 has been incorporated into clinical practice guidelines. The Infectious Diseases Society of America/American Thoracic Society guidelines, for instance, recommend that severity-of-illness scores, such as CURB-65, be used to identify patients with community-acquired pneumonia who may be candidates for outpatient treatment (strong recommendation, level 1 evidence).[2] They additionally recommend that severity-of-illness scores be supplemented with physician determination of subjective factors, ie,

Table 3. CURB-65 test characteristics at various score cut points.

	Sensitivity, %		Specificity, %	
CURB-65 Cut Point	Critical Care Intervention	Mortality	Critical Care Intervention	Mortality
≥1	94.2	96.9	23.2	21.4
≥2	78.4	92.8	54.8	51.8
≥3	41.4	44.3	90.2	86.8
≥4	13.7	11.3	98.8	97.4

ability to safely and reliably receive oral medications and appropriate resource availability (strong recommendation, level II evidence).[2] The British Thoracic Society guidelines suggest that patients who have a CURB-65 score of 0 or 1 are at low risk of death and may be suitable for outpatient treatment.[3] Moreover, the BTS guidelines state that "patients with a CURB-65 score of 0 have a low risk of death and do not normally require hospitalization." However, we found that 15.6% of patients with a CURB-65 score of 0 to 1 were admitted to the ICU and 6.4% received a critical care intervention. The guidelines further state that "patients with a score of 2 should be considered for short inpatient stay or hospital-supervised outpatient treatment." Yet our study demonstrates that 27.0% of patients with a CURB-65 score of 2 were admitted to the ICU and 15.4% received a critical care intervention.

The use of mortality as an endpoint for decisionmaking does not account for outcomes modified by inpatient care. As we have shown in our study, 85% of patients admitted to the hospital with pneumonia and greater than 60% admitted to the ICU have a CURB-65 score of 0 to 2, and although mortality is low, the need for critical care therapies is relatively high (10.1%). The rate of critical care intervention does not include other therapies that may contribute to increased survival such as supplemental oxygen for hypoxia, intravenous antibiotics, or a modest amount of intravenous fluids for hypotension. The need for clinical decision rules in pneumonia calibrated to proximal outcomes (as opposed to mortality) has been recently noted.[7]

As did the original study in which the CURB-65 score was derived,[4] we included only patients who were admitted to the hospital after presenting to the ED with pneumonia and did not include those discharged to home. Although this is how the original study was performed, we readily acknowledge that this approach is not appropriate when the safety of outpatient management is assessed and fails to take into account that mortality may be modified by inpatient care. A recent study of greater than 21,000 ED patients with community-acquired pneumonia (both admitted and discharged) found that although CURB-65 score

performed well in predicting mortality in discharged patients, rates of 7-day readmissions were relatively high: 4.2% for a CURB-65 score of 0 and 7.7% for a score of 1.[14] Moreover, rates of admission of patients with CURB-65 scores of 0 to 1 were substantial, at 36.2% and 66.9%, respectively, suggesting that physicians intuitively recognized that many patients with low scores likely needed inpatient care.

In our study, the sensitivity of CURB-65 score greater than or equal to 2 in predicting receipt of critical intervention in our cohort was 78%, suggesting that greater than 20% of patients presenting with pneumonia who ultimately require a critical care intervention might be classified as being at low risk and eligible for discharge. Although the AUROC was relatively high for critical care intervention, at 0.73, the CURB-65 score was not derived to prioritize sensitivity in an ED setting in which appropriate disposition and timely intervention are vital. The sensitivity for a CURB 65 score of greater than or equal to 3 for critical care intervention was quite low (41.4%), suggesting that many patients with low CURB-65 scores may need critical care interventions and highlighting the potential pitfalls of triaging patients to the ward on the basis of a low CURB-65 score. Consideration of specific test characteristics (ie, sensitivity, specificity, and positive and negative predictive value) as opposed to overall AUROC is critical when clinicians are considering the use of any clinical prediction tool for patients with potentially life-threatening conditions.[15-18]

Other studies have explored the need for certain critical care interventions in community-acquired pneumonia according to CURB-65 score. These studies were smaller than the present analysis and were less comprehensive with respect to included critical care interventions. In one study, 30 of 405 patients (7.4%) with a CURB-65 score of 0 to 1 required assisted ventilation or vasopressors, whereas just 5 died (1.2%).[19] Including the aforementioned study, the performance of CURB-65 score for predicting the need for vasopressor or ventilatory support has been explored in 3 studies, with a combined sensitivity of 57.2% and specificity of 77.2% at a cutoff of CURB-65 score greater than or equal to 3.[20] These findings are similar to those reported in our analysis.

The strengths of our study include the large sample size and availability of a high-temporal-resolution electronic ICU database. We used critical care intervention as a more proximal endpoint than mortality, as demonstrated in a previous study.[9] This is a novel endpoint that may be useful for future clinical decisionmaking tools for patients with pneumonia or other infections. Although we focused on critical care interventions in this study, other inpatient interventions (eg, intravenous antibiotics, guaranteed compliance with medications, supplemental oxygen) were not taken into account, and an even larger cohort of patients may have received some benefit from their care while hospitalized. Alternatively, we must highlight that whether receipt of critical care interventions leads to improved mortality among patients with pneumonia is unknown and beyond the scope of this project.

In summary, using CURB-65 score to support clinical decisionmaking based on 30-day mortality may classify as low risk patients who receive critical care interventions and ultimately survive. Patients in our study with low CURB-65 scores (0 to 2) were often admitted to the ICU and received critical care interventions. This finding highlights the need to consider the potential modifying effects of inpatient management on outcomes when applying clinical prediction tools tailored to mortality.

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All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REVIEW Open Access

Pre-hospital extra-corporeal cardiopulmonary resuscitation

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Abstract

Survival from out-of-hospital cardiac arrest (OHCA) has remained low despite advances in resuscitation science. Hospital-based extra-corporeal cardiopulmonary resuscitation (ECPR) is a novel use of an established technology that provides greater blood flow and oxygen delivery during cardiac arrest than closed chest compressions. Hospital-based ECPR is currently offered to selected OHCA patients in specialized centres. The interval between collapse and restoration of circulation is inversely associated with good clinical outcomes after ECPR. Pre-hospital delivery of ECPR concurrent with conventional resuscitation is one approach to shortening this interval and improving outcomes after OHCA. This article examines the background and rationale for pre-hospital ECPR; summarises the findings of a literature search for published evidence; and considers candidate selection, logistics, and complications for this complex intervention.

Keywords: Pre-hospital, Extracorporeal cardiopulmonary resuscitation, Extracorporeal membrane oxygenation, Extracorporeal life support

Backround and rationale

Survival to discharge from out-of-hospital cardiac arrest (OHCA) remains poor. In London overall reported survival is 9% for patients with out-of-hospital cardiac arrest and attempted resuscitation (31.5% for witnessed cardiac arrest with initial shockable rhythm) [1]. This mirrors a reported global OHCA survival rate of 2–11% with corresponding regional variation [2]. During conventional resuscitation, external chest compressions generate both coronary perfusion pressure and cardiac output [3, 4]. Coronary perfusion pressure dictates myocardial reperfusion, which in turn is critical to achieve return of spontaneous circulation (ROSC) [4]. Cardiac output dictates organ and cerebral perfusion, which is critical to prevent irreversible ischemic injury. The organ and cerebral perfusion delivered is influenced by a variety of factors, including the quality of chest compressions, body habitus, underlying comorbidities, and the aetiology of cardiac arrest. Optimal conventional cardiopulmonary resuscitation (CCPR) typically generates only a fraction of normal cardiac output (cardiac index ~ 0.6 L.min-1.m-2), commonly referred to as the 'low-flow' state [5]. A lengthy low-flow state during prolonged CCPR increases the risk of multi-organ failure and hypoxic brain injury after ROSC.

Extra-corporeal cardiopulmonary resuscitation (ECPR) is the implementation of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) during ongoing resuscitation attempts in cardiac arrest. In VA-ECMO, a venous drainage cannula is placed to drain blood which is then pumped through a membrane oxygenator before being returned under pressure into a central artery through a return cannula. There are various configurations of where cannulae can be placed, however the most common selection in cardiac arrest is a femoral vein drainage cannula and a femoral artery return cannula. Compared to CCPR, ECPR improves blood flow (cardiac index ~ 2.0 L.min-1.m-2) and oxygen delivery during cardiac arrest with the aim of preventing irreversible end-organ damage and hypoxic brain injury. It can also facilitate therapies such as coronary angiography or fibrinolysis to treat the primary cause of OHCA [6]. Although there are currently no published randomised trials of ECPR, observational evidence supports its use in carefully selected candidates [7].

A primary determinant of successful clinical outcomes after ECPR is the interval between collapse and onset of ECPR. This interval is further divided into 'no-flow time', the interval between collapse and onset of external chest

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compressions, and 'low-flow time', the interval between external chest compressions and onset of ECPR. Observational studies of ECPR for in-hospital cardiac arrest (IHCA) and OHCA highlight the importance of brief low-flow times. Survival to hospital discharge after ECPR for IHCA ranges from 20 to 35% [8, 9], whereas survival to hospital discharge after ECPR for OHCA is approximately 15% [10]. A key difference between these two populations is the longer low-flow intervals of CCPR in OHCA (as high as 80–155 min) [11–15]. A recent systematic review confirms that longer intervals of conventional resuscitation preceding ECPR (low-flow time) are associated with poor clinical outcomes (geometric mean ratio 0.90; 95% CI 0.81–0.99) [10].

During OHCA resuscitation, pre-hospital emergency care providers concentrate on optimizing CCPR and advanced life support, achieving ROSC, and identifying reversible causes of cardiac arrest. In the United Kingdom, CCPR typically lasts for a minimum of 20 min before resuscitation is terminated or the patient is transported to hospital with ongoing CPR [16]. Indeed, many guidelines advocate at least 20 min of resuscitation [17, 18]. Pre-hospital ECPR seeks to minimize low-flow time by delivering ECPR to the patient concurrently with initial CCPR. While posing unique logistical challenges, this strategy may shorten the delay to commencement of ECPR.

Hospital-based vs. pre-hospital ECPR for OHCA

In pre-hospital systems of care there is historical emphasis on resuscitation of OHCA patients on scene compared to the alternative strategy of early transport to hospital with ongoing resuscitation. This philosophy of remaining on scene is driven by the recognition that the best outcome for a patient in cardiac arrest is early ROSC, and the primary drivers of favourable outcome are high quality CPR and the treatment of reversible pathology. ROSC is most likely within the first few minutes of resuscitation, and if ROSC has not been achieved by 15 min of resuscitation there is only a 10–15% chance of subsequent good neurologic outcome [19, 20]. Since CPR quality degrades during patient extraction and transport to hospital, [21] many pre-hospital systems of care mandate a minimum resuscitation interval on scene before consideration of transport with CPR in progress. The only treatment offered at most hospitals is additional CCPR, and only 3–4% of patients survive when transported to hospital without ROSC [22, 23]. Some hospitals will consider fibrinolysis or coronary angiography with percutaneous coronary intervention in highly selected OHCA cases with ongoing CCPR [24]. Otherwise, ECPR offers the only novel additional therapy for patients transported to hospital after CCPR has failed. Hospital-based ECPR does offer a more controlled environment with immediate access to invasive monitoring, additional diagnostics, and additional therapeutic interventions to treat the underlying aetiology of cardiac arrest. However, hospital-based ECPR necessitates patient extraction, packaging, and transport, which all contribute to additional low-flow time and risk of subsequent multi-organ failure and hypoxic brain injury.

The ideal therapeutic window for ECPR is within 60 min after collapse [25]. Patients most likely to benefit from ECPR (e.g. younger age, witnessed, bystander CPR, shockable rhythm) also have the greatest probability of ROSC with CCPR during the first 10–15 min after collapse [20]. Pre-hospital systems of care with hospital-based ECPR need to factor in the time required for initial resuscitation efforts with CCPR on scene, time required for extraction and transport to hospital, the logistics of maintaining quality chest compressions en route to the hospital, and the procedural time needed to cannulate and initiate VA-ECMO. Some systems employ mechanical chest compression devices with early transport of potential ECPR patients to mitigate the degradation in CCPR quality and still allow sufficient time for VA-ECMO initiation at hospital [26]. Other systems deliver pre-hospital ECPR to the patient, eliminating the problems of CCPR during transport and attempting to decrease low-flow time compared to hospital-based ECPR [27].

Published evidence

We conducted a literature search of Medline to include English language papers that described the pre-hospital implementation of extracorporeal cardiopulmonary resuscitation. Search terms used were *extracorporeal cardiopulmonary resuscitation*, *prehospital* and *extracorporeal life support* and *extracorporeal membrane oxygenation*. In total, we reviewed 1108 titles to identify 65 potential abstracts that ultimately yielded six publications. We identified one additional case series abstract through a semi-structured internet search using the same search terms. Table 1 summarizes the published literature to date on prehospital ECPR.

Most published literature for pre-hospital ECPR comprises case studies and small case series. In total we found 88 reported cases of the pre-hospital implementation of ECPR with an overall survival rate of 15% (13/88). The sole cohort study by Lamhaut et al. in 2017 compared 2 periods of ECPR strategy in a before-and-after fashion. The initial strategy (period 1) involved a mandatory 30 min interval of CCPR before either transport to hospital (if within 20 min range) or initiation of pre-hospital ECPR. These logistical constraints resulted in a typical low-flow interval up to 90 min in duration, and this approach to pre-hospital ECPR yielded 8% survival with good neurological outcome. For context, the longest low-flow duration for any neurologically intact survivor in a recent multi-centre North American cohort of > 11,000 OHCA patients was 47 min [20]. The revised strategy (period 2) entailed a variety of

Table 1 Published literature on pre-hospital ECPR

Reference	Type of study	No. pre-hospital ECPR patients	Mean low flow interval
Arlt, et al. 2011 [47]	Case study	1	> 90 min
Lebreton, et al. 2011 [48]	Case study	1	60 min
Lamhaut, et al. 2012 [49]	Case study	1	60 min
Lamhaut, et al. 2013 [46]	Case series	7*	79 min
Hilker, et al. 2013 [50]	Case series	6	61 min
Lamhaut, et al. 2017 [51]	Case study	1	90 min
Lamhaut, et al. 2017 [27]	Before-and-after cohort study	46 (period 1) 27 (period 2)**	93 min (period 1)*** 71 min (period 2)***

*includes case reported in Lamhaut, et al. 2012. ** includes case reported in Lamhaut, et al. 2017. *** mean duration for all ECPR patients (47% prehospital ECPR vs. 53% hospital-based ECR). ECPR: extracorporeal cardiopulmonary resuscitation; min: minutes

modifications, notably a decision to initiate ECPR within 20 min of CCPR, and a greater emphasis on pre-hospital delivery of ECPR (unless the hospital was within 10 min range). Additionally, the selection criteria were more stringent, the ECPR team was dispatched as primary response to all OHCA cases < 70 years old, and epinephrine dosing was limited to a maximum of 5 mg. This revised strategy improved survival with good neurologic outcome to 29% (21% absolute increase), and the mean low-flow interval was reduced by 20 min. In propensity-matched analysis, pre-hospital ECPR had shorter low-flow intervals and higher rates of ROSC compared to hospital-based ECPR. There was no difference in survival, but the authors note the risk of a survival time bias in the hospital-based ECPR patients who had additional low-flow period during extraction, packaging, and transport to hospital [27].

Forthcoming prehospital ECPR trials

The first randomised prospective trial comparing two different strategies of delivering ECPR to OHCA patients (prehospital ECPR vs. hospital-based ECPR) is currently recruiting in France (ACPAR2; NCT02527031) with an estimated completion date of March 2019. Patients randomized to prehospital ECPR will receive ECPR between 20 and 30 min after collapse at the site of collapse. Those randomized to hospital-based ECPR will receive on-site CCPR and transfer to hospital for subsequent ECPR. The investigators hypothesize that a shorter low-flow period in the prehospital ECPR arm will translate into superior survival with good neurologic outcome. Selection criteria include a no-flow time < 5 mins, age 18–65 years, refractory arrest defined as 20 min of CCPR, and presence of shockable rhythm or signs of life during resuscitation [28]. A search of clinicaltrials.gov demonstrates no other current pre-hospital ECPR trials. There are three other hospital-based ECPR trials (NCT01511666, NCT02832752, NCT03065647) that may yield data that is extrapolated to pre-hospital ECPR.

Patient selection

Successful outcomes after ECPR largely depend on appropriate candidate selection. Most OHCA patients will not be candidates for pre-hospital ECPR. Multiple observational studies have identified consistent prognostic factors in OHCA patients that are most likely to benefit from hospital-based ECPR. The precise sensitivity and specificity of each of these criteria are still undefined, as is the product of relaxing specific criteria. These prognostic factors can be extrapolated to select suitable candidates for pre-hospital ECPR (Table 2). Relaxation of these inclusion criteria may yield additional patients that benefit from pre-hospital ECPR, but will almost certainly reduce the overall neurologically intact survival rate. Absent from this list is some evidence-based consideration of baseline functional status, including overall health, comorbidities, quality of life, cognition, independence, etc. These aspects are important, but there is little data to guide clinicians towards a reliable and valid means to assess these intangible factors in the acute setting when considering ECPR.

Age

Age is an established prognostic factor in OHCA after CCPR. There is an inverse relationship between age and likelihood of survival or good neurologic outcome, and a progressive decline in likelihood of good outcome after

Table 2 Suggested Criteria for Pre-Hospital ECPR Selection

Inclusion Criteria for Consideration of Pre-hospital ECPR:

1. Age 18–65 years
2. Witnessed arrest with bystander CPR
3. VF/VT Rhythm or signs of life during resuscitation*
4. No-flow time < 5 min
5. Ability to initiate ECPR within 60 min of collapse

*signs of life include attempted respiratory effort, gasps, movement, or pupil reactivity. *ECPR* extracorporeal cardiopulmonary resuscitation, *CPR* cardiopulmonary resuscitation, *VF* ventricular fibrillation, *VT* ventricular tachycardia

64 years [29]. Several ECMO centres have used an upper age limit of 75 years as a selection criterion for hospital-based ECPR [30–32]. A recent Parisian pre-hospital OHCA ECPR cohort study used an upper age limit of 70 years, although the median age of patients was 51 years and only 23% of patients were more than 60 years old [27]. An Australian mixed IHCA and OHCA cohort used an upper age limit of 65 years and the median age of patients was 52 years [26]. An association between age and favourable outcome has not yet been established in ECPR observational studies for OHCA [10]. It is often difficult to accurately assess age in OHCA. Until better evidence is available, 65 years appears to be a reasonable upper limit for pre-hospital ECPR. (We do note the distinction between 'chronologic' age and 'physiologic' age as a function of comorbidities and overall health, and acknowledge that prehospital ECPR could benefit some patients older than 65 years). Hospital-based ECPR is employed in paediatric patients, most commonly those with IHCA and/or known heart disease [33, 34]. There is no evidence on the inclusion of paediatric patients in pre-hospital ECPR programs. While the anatomy and physiology of some teenagers may be similar to those of young adults, at some point inclusion of younger age groups requires additional paediatric-specific training in VA-ECMO.

Witnessed arrest and bystander CPR

Witnessed collapse and bystander CPR are both positive prognostic factors in OHCA after CCPR [35], especially in cases of prolonged resuscitation [19]. These prognostic factors have incompletely translated to ECPR, because firm conclusions are limited by the small number of studies and variable reporting methods [10]. Both factors highlight the issue of 'no-flow' time, which is critical because neuronal cell death begins within minutes of loss of cerebral oxygen delivery [36]. Most ECPR centres use unwitnessed events or 'no-flow' interval > 5 min as exclusion criteria [27, 32]. The case details of witnessed collapse and bystander CPR can often be established on scene, so witnessed collapse with initiation of bystander CPR within 5 min are reasonable selection criteria for pre-hospital ECPR.

Cardiac rhythm

Shockable initial cardiac rhythm (ventricular fibrillation or pulseless ventricular tachycardia) is a major prognostic factor for OHCA and has been used as an inclusion criterion for ECPR [12]. A recent systematic review found that shockable initial cardiac rhythm is associated with favourable clinical outcomes after ECPR for OHCA (summary odds ratio 2.20; 95% CI 1.30–3.72) [10]. Asystole has significant negative prognostic value, and is often an exclusion criterion for ECPR. Pulseless electrical activity (PEA) represents a clinical challenge to the clinician. It is often grouped together with asystole as a non-shockable rhythm, and is commonly regarded as a negative prognostic factor. However PEA cardiac arrests of certain aetiologies are reversible and carry a good prognosis with ECPR (e.g. pulmonary embolism, environmental hypothermia) [37, 38]. Additionally, PEA can actually reflect different physiologic states: complete electro-mechanical dissociation with cardiac standstill and residual electrical activity, or impaired circulation with preserved cardiac motion but no palpable pulses. The former is unlikely to respond to ECPR, but the latter is very treatable with ECPR given a reversible aetiology. A pragmatic approach may be to include any subject with organized electrical activity and exclude asystole. Alternatively, patients with signs of life (e.g. respiratory efforts or agonal breaths, patient movement, or pupillary light reactivity) could be included irrespective of rhythm. The latter combination of selection criteria was utilized in the recent Parisian pre-hospital ECPR cohort study [27]. Notably, in that cohort there were no ECPR survivors that did not demonstrate some signs of life during CCPR prior to ECPR initiation.

Low flow duration

The prognostic value of low-flow duration is well established for ECPR after both IHCA and OHCA. Among IHCA cases, overall survival after ECPR was 30–40% with low-flow times < 60 min, and only 15–20% with low-flow times > 60 min [25, 30]. A recent systematic review found that low-flow duration was inversely associated with favourable outcome after ECPR (summary geometric mean ratio 0.90; 95% CI 0.81–0.99) [10]. Low-flow time may be the most important factor that differentiates the higher survival after ECPR observed for IHCA compared to OHCA [39]. This is consistent with the strong physiological argument that a longer low-flow time risks irreversible multi-organ failure and hypoxic brain injury, negating the potential benefits of ECPR. A collapse to ECPR interval no longer than 60 min is a common selection criterion at many ECMO centres [40, 41]. Since the fundamental justification for pre- hospital ECPR is reducing the low-flow interval, it should be as brief as possible and not exceed 60 min.

Timing of ECPR initiation

Given the adverse effects of 'low-flow' time, it would seem reasonable to initiate ECPR as soon as possible after collapse in eligible candidates. However, initiating ECPR too early in the resuscitation exposes patients to invasive procedures with significant complications and unproven outcome benefits when a significant proportion will achieve ROSC within the initial minutes of CCPR. Furthermore, distracting from the emphasis on continuous, high-quality chest compressions is potentially harmful [42]. Yet traditional resuscitation most often fails, and the likelihood of ROSC steadily decreases with elapsed durations of CCPR

[43]. At what elapsed interval of CCPR do the potential benefits of ECPR outweigh the procedural risks and the likelihood of failed CCPR? Common practice is to require 20–30 min of CCPR before declaring OHCA 'refractory' and initiating ECPR [27, 44]. However, based on the natural history of large North American cohorts of OHCA cases, it is reasonable to shift from CCPR to ECPR after 10–20 min of CCPR [19, 20]. This window strikes the best balance between maximizing outcomes with CCPR (~ 90% of patients with eventual good neurologic outcome had achieved ROSC) and recognizing the time constraints of the therapeutic window for ECPR.

Logistical considerations

The logistics for providing a pre-hospital ECPR service are complex and intimidating. For optimal results and the shortest low-flow times, the pre-hospital ECPR team should be a primary response to out-of-hospital cardiac arrests (i.e. dispatched at the time of the initial emergency service call, rather than as a secondary response once cardiac arrest has been confirmed by on-scene emergency services) [27]. This necessitates screening all collapse, unresponsive, and cardiac arrest calls made to emergency services, identifying those calls most likely to meet inclusion criteria, and dispatching an ECPR team concurrently with standard pre-hospital resources. Given the limited pool of ECPR-trained personnel, a single ECPR team may have to serve a large geographical area. For example, London Ambulance Service attended 10,116 out-of-hospital cardiac arrests in 2015–2016. Of these, 560 (5.5%) were witnessed events with bystander CPR and an initially shockable cardiac rhythm – cases most likely to meet ECPR selection criteria [45]. This provides a tremendous challenge for dispatchers trying to identify the approximate 1 in 20 arrests that meet only some of the criteria for consideration of ECPR. In order to capture suitable cases, some degree of over-triage is inevitable. Thus, the logistics of pre-hospital ECPR may be most suited to an urban environment where a fast response ground vehicle could transport the ECPR team and equipment with a target response time within 10 min. However, given the resources required, prehospital ECPR is likely not practical or even feasible in all metropolitan regions. The rural environment provides significant barriers to pre-hospital ECPR, where ground-based response frequently lasts 20–30 min or longer to get to scene, negating the reduction in low-flow interval sought with pre-hospital ECPR. Integration with helicopter emergency medical teams (HEMS) and transport by rotatory wing aircraft may achieve faster dispatch-to-scene intervals, but would be a substantial resource burden given the inevitable over-triage of the ECPR team to cases ultimately not suitable for ECPR. The selective targeting of large population high risk events such as marathons with an ECPR team is a potential trade off between resource allocation and likely patient benefit.

The financial costs of pre-hospital ECPR are high: this includes both fixed and variable costs of equipment and personnel, as well the expectation that there will be attendance at OHCA cases ultimately deemed not suitable for ECPR. The required personnel for pre-hospital ECPR varies at different institutions, but would commonly include at a minimum two consultant-level specialists and a clinical perfusionist. Future anticipated technological advancements and concurrent reductions in the complexity of priming a VA-ECMO circuit and preparing a console may allow change in both the required seniority of specialists and number of team members. However, the availability of pre-hospital physicians integrated into the emergency medical response will likely be a pre-requisite for such a complex intervention, limiting pre-hospital ECPR implementation to countries and healthcare systems where this occurs.

We have estimated costs of approximately 880,000 Euros a year to provide an equipped primary response ECPR team for 9 h a day, 7 days a week. Other cost considerations include the environmental and human factor issues involved in the pre-hospital environment. Hospital-based physicians may not be used to performing complex clinical tasks and procedural steps in a variety of pre-hospital environments, and may struggle to integrate into established pre-hospital emergency response teams. Such procedural tasks include establishing a sterile field and cannulating femoral vessels. Percutaneous and surgical cut-down techniques have been described, and the choice of technique may be made on clinical circumstance and team experience. After insertion, optimizing circulatory flow and ensuring adequate systemic vascular resistance is challenging in the absence of invasive hemodynamic monitoring. Pre-hospital ECPR teams may have to titrate circuit settings and medication infusions to venous oxygenation saturations until arrival at hospital. Pre-hospital and human factor training may be necessary, which adds additional costs and resources.

Discussion of cost raises the larger economic questions of whether pre-hospital ECPR is more or less cost effective than other endeavours to improve survival after OHCA, including public education campaigns to increase the prevalence of bystander CPR provision and use of an automated external defibrillator ('AED'). Direct comparisons of cost effectiveness are not possible until the cost effectiveness of ECPR has been fully evaluated. As with any other complex and costly intervention, opportunity cost ought to be discussed.

Complications

There are many anticipated complications when delivering a complex procedure in the pre-hospital environment (Table 3). All hospital-based complications of ECPR are

Table 3 Common complications of prehospital ECPR

Complication	Specific Pre-hospital Concerns
Vascular injury and Bleeding	Availability of pre-hospital blood products, difficulty recognising complications such as retroperitoneal bleeding. No access to interventional radiology or operating theatres.
Failure to cannulate	Hospital-based percutaneous VA-ECMO cannulation has a reported failure rate between 7% and 10% [52, 53] and is anticipated to be higher in the pre-hospital environment. Surgical cut down may reduce the expected failure rate in the pre-hospital setting.
Limb Ischaemia	In-hospital limb ischaemia after insertion of VA-ECMO cannulae is reported in the range of 12–15% [31, 52] and would be similar in the pre-hospital environment. The usual practice of inserting a retrograde distal limb perfusion cannula would be deferred until arrival at hospital. One alternative could be using smaller calibre arterial cannulae accepting either lower flows or higher pressures.
Infection	Although the true infection rate related to ECMO cannulae insertion is unknown, ECMO is an independent risk factor of blood stream infection. [54] Pre-hospital ECMO insertion will not be as clean as an operating theatre and the infection risk may be increased.

ECPR extracorporeal cardiopulmonary resuscitation, *VA-ECMO* veno-arterial extracorporeal membranous oxygenation, *ECMO* extracorporeal membranous oxygenation

present along with additional risks specific to the pre-hospital environment. The sole pre-hospital ECMO-related complication reported to date is a case of accidental cannula displacement [46].

Conclusion

Pre-hospital ECPR seeks to address the physiological rationale and observational data supporting the reduction of low-flow time as much as possible to improve survival and good functional outcome after OHCA. Forthcoming prospective trials of pre-hospital ECPR (NCT02527031) and hospital-based ECPR (NCT01511666, NCT02832752, NCT03065647) will aid in refining selection criteria and identifying which patients may benefit from pre-hospital ECPR compared to hospital-based ECPR or CCPR. The ideal dispatch and deployment strategy for pre-hospital ECPR teams has yet to be determined, and will likely depend on unique features of each pre-hospital system of care. The clinical benefits of rapid response and shorter low-flow time need to be balanced with the costs of over-triage and resource utilization. A deeper understanding of the health economics surrounding pre-hospital ECPR is also required to justify the large resource requirement. In summary, more evidence is required and regional systems of care deploying pre-hospital ECPR are encouraged to publish prospectively collected data on their protocols, process measures, and outcomes. Despite its challenges, pre-hospital ECPR offers the potential to dramatically improve clinical outcomes for a subset of OHCA patients.

Abbreviations

CCPR: Conventional Cardiopulmonary Resuscitation; CPR: Cardio-pulmonary Resuscitation; ECLS: Extracorporeal Life Support; ECMO: Extracorporeal Membrane Oxygenation; ECPR: Extracorporeal Cardio-pulmonary Resuscitation; ELSO: Extracorporeal Life Support Organisation; IHCA: In Hospital Cardiac Arrest; OHCA: Out of Hospital Cardiac Arrest; PCI: Percutaneous Coronary Intervention; ROSC: Return of Spontaneous Circulation; VA-ECMO: Veno-arterial Extracorporeal Membrane Oxygenation; VF: Ventricular Fibrillation; VT: Ventricular Tachycardia

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DL and BOB developed the idea and scope for the review. BS conducted the literature review and drafted the manuscript. All authors contributed to revising and editing the manuscript for content. All authors read and approved the final manuscript.

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Prevalence of potentially inappropriate prescribing in older people in primary care and its association with hospital admission: longitudinal study

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ABSTRACT

OBJECTIVE

To determine whether hospital admission is associated with potentially inappropriate prescribing among older primary care patients (aged ≥65 years) and whether such prescribing was more likely after hospital admission than before.

DESIGN

Longitudinal study of retrospectively extracted data from general practice records.

SETTING

44 general practices in Ireland in 2012-15.

PARTICIPANTS

Adults aged 65 years or over attending participating practices.

EXPOSURE

Admission to hospital (any hospital admission versus none, and post-admission versus pre-admission).

MAIN OUTCOME MEASURES

Prevalence of potentially inappropriate prescribing assessed using 45 criteria from the Screening Tool for Older Persons' Prescription (STOPP) version 2, analysed both as rate of distinct potentially inappropriate prescribing criteria met (stratified Cox regression) and binary presence of potentially inappropriate prescribing (logistic regression) and adjusted for patients' characteristics. A sensitivity analysis used matching with propensity scores based on patients' characteristics and diagnoses.

RESULTS

Overall 38 229 patients were included, and during 2012 the mean age was 76.8 (SD 8.2) years and 43% (13 212) were male. Each year, 10.4-15.0% (3015/29 077 in 2015 to 4537/30 231 in 2014) of patients had at least one hospital admission. The overall prevalence of potentially inappropriate prescribing ranged from 45.3% (13 940/30 789) of patients in 2012 to 51.0% (14 823/29 077) in 2015. Independently of age, sex, number of prescription items, comorbidity, and health cover, hospital admission was associated with a higher rate of distinct potentially inappropriate prescribing criteria met; the adjusted hazard ratio for hospital admission was 1.24 (95% confidence interval 1.20 to 1.28). Among participants who were admitted to hospital, the likelihood of potentially inappropriate prescribing after admission was higher than before admission, independent of patients' characteristics; the adjusted odds ratio for after hospital admission was 1.72 (1.63 to 1.84). Analysis of propensity score matched pairs showed a slight reduction in the hazard ratio for hospital admission to 1.22 (1.18 to 1.25).

CONCLUSION

Hospital admission was independently associated with potentially inappropriate prescribing. It is important to determine how hospital admission may affect appropriateness of prescribing for older people and how potential adverse consequences of admission can be minimised.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Potentially inappropriate prescribing is common among older people

It is associated with adverse outcomes including emergency hospital attendances and admissions, adverse drug events, and poorer quality of life

Research to date has focused on characteristics of patients and general practitioners as risk factors for poor prescribing quality

WHAT THIS STUDY ADDS

Hospital admission was independently associated with an increased rate of potentially inappropriate prescriptions

Patients who were admitted to hospital were more likely to have potentially inappropriate prescribing after admission compared with before, independent of patients' characteristics

This illustrates the need to consider and overcome potential adverse effects of hospital admission on appropriateness of prescribing among older patients

Introduction

Adults aged 65 years and over are a growing population and represent the largest consumers of prescribed drugs.[1 2] Although optimal prescribing aims to maximise benefits to patients while minimising harms and costs, achieving this balance when caring for older patients in primary care can be challenging. Physiological changes in ageing can impair metabolism and excretion of drugs and increase sensitivity to their effects.[3] In addition, older patients tend to have a higher burden of multimorbidity and so take more drugs, contributing to both increased treatment burden and potential drug-drug and drug-disease interactions.[4] Lastly, although most prescribing in primary care is repeat prescribing,[5] such drugs are often initially prescribed in secondary care, which can be problematic as the general practitioner is responsible for coordination and managing all prescriptions.[6] This can be even more challenging for patients with multimorbidity who attend multiple healthcare providers.

Use of prescribed drugs among older adults is increasing despite the high risk of adverse drug events and resultant morbidity and mortality.[1 2 7] A recent

systematic review focusing on adverse drug events in ambulatory care found prevalence rates ranging from 2.8% to 34.7%, up to a quarter of which were judged to be preventable.[8] Another systematic review reported that 9.9% of all hospital admissions in people aged 65 years or over were as a result of an adverse drug event.[9]

Appropriateness of prescribing can be assessed by process measures (that is, what providers do) or outcome measures (that is, patient outcomes). These measures can be either implicit (judgment based) or, more often, explicit (criterion based).[10] Examples of explicit measures include the Beers criteria and the Screening Tool of Older Person's potentially inappropriate Prescribing (STOPP) and Screening Tool to Alert doctors to the Right Treatment (START).[11] Explicit measures have the advantage of being based on literature review and expert consensus, and they are reliable and have content validity, although they do periodically need revision to reflect new evidence. In 2015 the STOPP/START criteria were updated to add new criteria and remove obsolete ones.[11] In STOPP/START 2, the final list of 114 criteria, including 80 STOPP criteria and 34 START criteria, was agreed after two rounds of Delphi validation.[11] The STOPP/START 2 criteria can be used to examine potentially inappropriate prescribing in older people.

The adverse outcomes associated with the STOPP criteria are well established, including adverse drug events, emergency admissions or emergency department visits, and poorer quality of life.[12-15] Previous studies have examined predictors of potentially inappropriate prescribing, such as patients' characteristics (for example, multimorbidity, age, and number of prescribed drugs), and characteristics of general practices (for example, deprivation of catchment area).[16 17] There has been less focus on how health system factors, such as hospital admission or care transitions, may contribute to the appropriateness of prescribing for ambulatory care patients.

Therefore, the objectives of this study were to use the revised STOPP criteria to estimate the annual prevalence of potentially inappropriate prescribing in older community dwelling people in Ireland, to examine any association between hospital admission and potentially inappropriate prescribing, and to compare the prevalence of potentially inappropriate prescribing before and after hospital admission. We hypothesised that occurrence of potentially inappropriate prescribing among older adults may be significantly associated with hospital admission and, among patients who were admitted to hospital, occurrence of potentially inappropriate prescribing may differ before and after admission.

Methods

Study population and study design

This was a longitudinal study using a retrospectively collected dataset that included general practitioners' patients aged 65 years or over between 2012 and 2015. We used the patient management system Socrates (www.socrates.ie) to collect data from 44 general practices in Ireland, including prescribing, demographic, clinical, and hospital admission records. Socrates is one of four electronic health record vendor systems accredited by the Irish College of General Practitioners. Most (94%) general practices in Ireland are computerised, and electronic morbidity coding and prescribing occurs in more than 90% of these computerised practices.[18] Although the validity of morbidity recording in Ireland is not as good as in the UK, recent initiatives have improved both completeness and validity of morbidity coding.[19] Socrates has created quality indicator tools used for audit and also in research, such as a study of resistance patterns of urinary tract infections.[20] The STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement was used in the conduct and reporting of this study.[21]

Explanatory variables and outcomes of interest

We identified potentially inappropriate prescribing, according to 45 STOPP 2 criteria, by using information on drugs and diagnoses for each patient in the dataset, in each of the four years. A total of 35 (44%) criteria could not be applied—for example, owing to lack of information on laboratory monitoring, history of falls, or prescribing indication (see appendix 1). Where necessary, we included prescribing and diagnosis information from before 2012 when estimating the prevalence of potentially inappropriate prescribing—for example, for criteria relating to first line treatment. An extensive description of criteria and their application is provided in appendix 2. For each patient, we calculated the total number and dates of first occurrence of distinct potentially inappropriate prescribing criteria met per calendar year. We analysed these either as recurrent events (that is, rate of distinct potentially inappropriate prescribing criteria met per year) or as a dichotomous variable (at least one potentially inappropriate prescription in the period considered or no event).

The STOPP criteria, as explicit measures of inappropriate prescribing, have been used extensively in research as measures of the process of care. Their validity has been established in multiple studies showing their relation with important outcomes for patients. In terms of predictive validity, STOPP modestly discriminates for outcomes such as adverse drug events, emergency department visits, and hospital admissions (C indices of 0.65-0.70).[22] Other observational studies have found consistent associations between the STOPP criteria and avoidable adverse drug events relevant to the index admission among hospital inpatients,[12] poorer quality of life,[14] emergency department visits,[14 15] and unplanned readmission to hospital.[23] Prescribing included in STOPP was considered causal in 30% of adverse drug reactions in a Swedish study in an older population,[24] and in a study of definitely or possibly avoidable adverse drug events that led to hospital admission, 62.2% were listed in the STOPP criteria.[12] On this basis, the STOPP criteria can be considered a valid process

measure of quality of care, and they have been used as primary outcomes in interventional trials aiming to improve prescribing.[25 26]

To examine the association between hospital admission and potentially inappropriate prescribing, we defined the explanatory variable hospital admission as a dichotomous variable (no hospital admission versus any admission). Hospital admission was incorporated as a time dependent variable in the Cox model, considered as "no hospital admission" before the date of the first admission and "hospital admission" after that date. All practices included elective and emergency admissions to public hospitals, and four of the 44 practices additionally included emergency department attendances. For the comparison of potentially inappropriate prescribing before and after hospital admission, the explanatory variable was time period (after hospital admission versus before). The post-admission period started on the day after hospital admission. For those patients admitted more than once in the same year, we considered only the first admission.

Categorical covariates adjusted for in all models were sex and type of health cover (with four categories: General Medical Services (GMS) scheme, Doctor Visit Card (DVC), private patient, and other). Continuous covariates were age (years), number of prescription items in that period, and multimorbidity. The GMS and DVC schemes are types of public health coverage, providing eligible patients with a range of health services including general practitioner visits free of charge. These are means tested, with eligibility based on household income and age. The GMS scheme covers the most socioeconomically deprived people, approximately one third of the population, and 90% of those aged 70 years or over, for whom a lower income threshold applies.[27] The DVC scheme covers people with higher, but still limited, means. Other people pay out-of-pocket for primary care services such as general practitioner visits and drugs; hence Ireland has a mixed public-private healthcare system. We assessed the number of prescription items as the total number of items prescribed to a patient per year, not accounting for multiple issues/repeats on prescriptions. We assessed multimorbidity by using the Charlson comorbidity index.[28] This index is based on 17 conditions weighted by one year mortality risk, and a higher score indicates more severe comorbidity.

Statistical analyses

Annual prevalence of potentially inappropriate prescribing

We described demographic and clinical characteristics of patients (such as age, sex, health cover type, number of prescription items, and multimorbidity) and the overall prevalence of potentially inappropriate prescribing for each year considered. Data are expressed as mean (standard deviation), median (interquartile range), and proportions (absolute and relative frequencies) as appropriate. Analyses were run on a complete case basis, and the numbers of people included in each analysis are reported in the relevant tables and figures.

Association between potentially inappropriate prescribing and hospital admission

We examined the relation between potentially inappropriate prescribing and hospital admission adjusted for age, sex, health cover type, number of prescription items, and multimorbidity. We fitted both a mixed effect logistic regression model (in which the outcome was defined as dichotomous (0 without any potentially inappropriate prescribing in that year, or 1 otherwise)) and the Prentice, Williams, and Peterson (PWP) model (in which the outcome was time from the beginning of the year to a new potentially inappropriate prescribing criterion observed in each patient per calendar year). The mixed effect logistic regression model extends the general linear model by incorporating correlations among the outcomes (multiple observations per patient). This can be accomplished by including random effects. In this study, we introduced two random effects representing the patient and the year. We used the MCMCglmm package in R,[29 30] because models obtained using the glmer function of the lme4 package did not converge. Modelling of the rate of distinct potentially inappropriate prescribing events used the PWP model,[31] which is an extension of the Cox proportional hazard model. We used a stratum variable to keep track of the number of previous potentially inappropriate prescribing criteria met, allowing the hazard for a new potentially inappropriate prescribing criterion to change after a previous event. We used a robust variance estimator to account for individual patients' heterogeneity.[32] We included hospital admission as a time dependent variable that could change from "no hospital admission" to "hospital admission" during each year. We did a stratified analysis for health cover type because the proportional hazard assumption was not satisfied. We obtained an overall hazard ratio for the whole study period, also stratifying by year. As the date of death was not included in the dataset, within each year the length of follow-up was until the end of the year if the patient had a record in the following year or up until the date of the last prescription in that year if not. We used the survival package in R for this analysis.[33] To avoid double counting, we omitted criterion 32 from this analysis because it overlapped fully with criterion 1 (both relate to long term use of non-steroidal anti-inflammatory drugs; see appendix 2 for further details).

Potentially inappropriate prescribing before and after admission to hospital

We did a second analysis comparing potentially inappropriate prescribing before and after hospital admission among only those patients who were admitted to hospital during a study year. Paired sample tests (that is, having two observations per patient: one for presence/absence of potentially inappropriate prescribing before hospital admission

and one for after admission) allowed the temporality of the relation between hospital admission and potentially inappropriate prescribing to be assessed and also accounted for between patient variability. We fitted a mixed effect logistic regression model and included a random intercept for each patient to allow between patient variability in the outcome and for each year, using the MCMCglmm package in R.[30] The outcome was whether or not the patient had any potentially inappropriate prescribing event in the time period considered. The explanatory variable was time period (after hospital admission, relative to before admission), with adjustments made for the covariates listed above. In all analyses, we defined P<0.05 as statistically significant.

Sensitivity analyses

Firstly, we repeated each of the above analyses separately by calendar year to assess the consistency of observed associations over the study period. Secondly, owing to some missing data for the Charlson comorbidity index, we also repeated analyses using an alternative measure of multimorbidity. We used RxRisk-V, a prescription based measure of morbidity including medication proxies for 45 conditions, which has shown criterion validity and reliability compared with patients' medical diagnoses.[34] Prescription data were available for all included participants, and RxRisk was adjusted for in models as a binary indicator of multimorbidity (that is, two or more conditions).

Lastly, as patients were not randomly allocated to being admitted to hospital or not, these groups may have differences in their characteristics that could bias estimates. We did a sensitivity analysis using propensity score matching to assess whether the association between hospital admission and potentially inappropriate prescribing could be due to unmeasured confounders.[35] We used the propensity score, defined as the conditional probability of hospital admission given the measured covariates, to balance covariates in the two groups. Using the MatchIt package in R,[36] we first fitted a logistic regression model to estimate propensity scores. We modelled the conditional probability of hospital admission as a function of baseline and those clinical characteristics associated with admission that were also independent risk factors for potentially inappropriate prescribing. These variables included age, sex, health cover type, number of prescription items, Charlson comorbidity index, and whether the patient had been diagnosed as having any of the five most common conditions (diabetes, chronic obstructive pulmonary disease, any type of tumour, a myocardial infraction, or cerebrovascular disease). We randomly selected each patient with a hospital admission and then matched them with the patient with no admission with the closest propensity score. Finally, we fitted the same models considering only the matched pairs.

Patient involvement

Patients were not involved in the conception, design, or conduct of this research. We plan to disseminate the findings to the public and patients through our contacts in patient representative bodies, the popular media, and the participating general practices.

Results

Descriptive statistics

A total of 38 229 patients were included in the dataset over the period 2012 to 2015. Table 1 shows demographics and clinical characteristics of this sample, by year. We excluded patients without prescriptions during the period analysed. During 2012, the mean age of included patients was 76.8 (SD 8.2) years and 43% were male. For each study year, 10.4-15.0% of patients had at least one hospital admission.

Annual prevalence of potentially inappropriate prescribing

The overall prevalence of potentially inappropriate prescribing ranged from 45.3% (13 940/30 789) of patients in 2012 to 51.0% (14 823/29 077) in 2015 (appendix 3). The individual criteria with the highest prevalence in 2015 included proton pump inhibitor for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for more than eight weeks (7836; 26.9%), benzodiazepines for at least four weeks (5562; 19.1%), and drugs prescribed beyond the recommended duration (3988; 13.7%, primarily driven by Z drug hypnotics (zolpidem, and

Table 1 | Demographics and main clinical characteristics by year. Values are numbers (percentages) unless stated otherwise

Demographic and clinical characteristics	2012 (n=30 753)	2013 (n=30 789)	2014 (n=30 231)	2015 (n=29 077)	Missing data (%)
Mean (SD) age, years	76.8 (8.2)	76.4 (8.1)	75.9 (7.8)	75.0 (7.6)	0.08
Male sex	13 212 (43.0)	13 335 (43.3)	13 176 (43.6)	12 687 (43.6)	0.08
Patients with hospital admission	4151 (13.5)	4496 (14.6)	4537 (15.0)	3015 (10.4)	0
Health cover:					
General Medical Services scheme	21 053 (68.5)	21 472 (69.7)	21 202 (70.1)	20 859 (71.7)	
Doctor Visit Card	3029 (9.8)	3153 (10.2)	3201 (10.6)	3280 (11.3)	0.03
Private patients	6518 (21.2)	6004 (19.5)	5705 (18.9)	4817 (16.6)	
Other	153 (0.5)	160 (0.5)	123 (0.4)	71 (0.2)	
Median (interquartile range) prescription items per patient	22 (9-42)	22 (9-43)	23 (10-44)	21 (9-40)	0
Mean (SD) Charlson comorbidity index	0.89 (1.23)	0.94 (1.27)	1 (1.31)	1 (1.31)	24.2
Prevalence of potentially inappropriate prescribing events:					
1	6452 (21.0)	6843 (22.2)	6771 (22.4)	6857 (23.6)	0
2	4171 (13.6)	4254 (13.8)	4429 (14.6)	4220 (14.5)	
≥3	3317 (10.8)	3654 (11.9)	3762 (12.4)	3746 (12.9)	

zopiclone) for more than four weeks), and this was observed in each calendar year (appendix 3).

Association between potentially inappropriate prescribing and hospital admission

In the PWP regression model, hospital admission, higher age, greater number of prescription items, and multimorbidity were all associated with a higher rate of potentially inappropriate prescribing events. The rate of distinct criteria met per year increased by 24% if a patient had been admitted to hospital (hazard ratio 1.24, 95% confidence interval 1.20 to 1.28) when controlled for the other covariates (fig 1). For sex, the rate of potentially inappropriate prescribing criteria met per year was approximately 12% lower for men (hazard ratio 0.88, 0.87 to 0.89). The rate of distinct potentially inappropriate prescribing criteria observed in one year also increased as age, number of prescription items, and multimorbidity increased.

Results obtained from the mixed effect logistic regression model were analogous, although in this model age was not significant (see appendix 4). The odds ratio for hospital admission was 1.49 (1.42 to 1.58)—that is, the probability of at least one potentially inappropriate prescription during a year increased by 49% for patients admitted to hospital, after adjustment for relevant covariates.

Potentially inappropriate prescribing before and after admission to hospital

Having analysed potentially inappropriate prescribing in patients who were admitted to hospital compared with those who were not, we determined the effect of admission on a patient's likelihood of having potentially inappropriate prescribing among only those patients who were admitted. Figure 2 shows the estimated odds ratios with 95% credible intervals. Among patients who had at least one hospital admission in a year, the risk of having any potentially inappropriate prescription increased by 72% after admission to hospital. Women and patients with greater numbers of prescription items were more likely to have potentially inappropriate prescriptions.

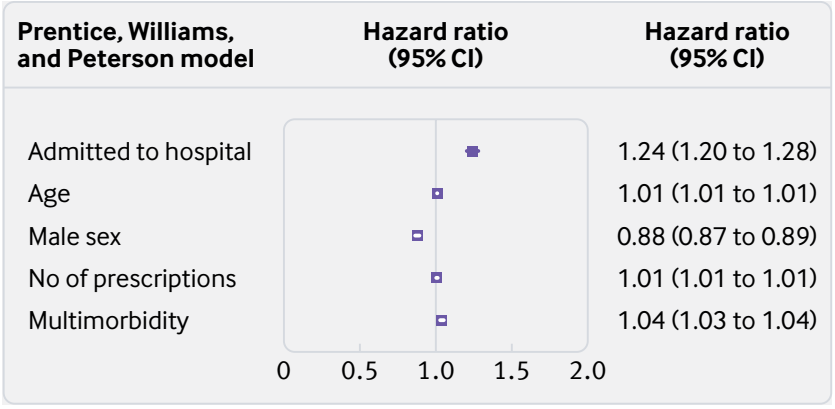

Fig 1 | Estimated hazard ratios (95% CI) for rate of distinct potentially inappropriate prescribing criteria met among all participants. Reference groups were no hospital admission and female sex

Sensitivity analysis

When analyses were repeated on a year by year basis, the relation between hospital admission and potentially inappropriate prescribing was consistent over time (appendix 5). Adjustment for multimorbidity using RxRisk instead of the Charlson comorbidity index (table 2), and therefore inclusion of participants for whom diagnostic coding may have been missing, resulted in little change in the magnitude of the parameter estimates for hospital admission. Lastly, propensity score matching compared patients admitted to hospital with those who were not admitted, using both the PWP model (fig 3) and the logistic model (appendix 6). These analyses still showed a statistically significant association between hospital admission and the outcome of potentially inappropriate prescribing (adjusted hazard ratio 1.22, 1.18 to 1.25; adjusted odds ratio 1.48, 1.37 to 1.58).

Discussion

This study found that a substantial proportion of community dwelling older people had at least one potentially inappropriate prescription defined according to the STOPP 2 criteria and that hospital admission was a significant marker of potentially inappropriate prescribing. Set against a general increase in potentially inappropriate prescribing and patients with multiple potentially inappropriate prescribing criteria met, we determined that after control for the characteristics assessed in this study (such as age, number of prescriptions, and multimorbidity) hospital admission was associated with a higher rate of potentially inappropriate prescribing. Furthermore, for patients who were admitted to hospital, their likelihood of having potentially inappropriate prescribing increased by 72% after admission compared with before, independent of other patient related factors. These relations were consistent across study years and were robust to different analytical approaches in sensitivity analyses.

Strengths and weaknesses of study

This study included a large sample of community dwelling older adults and used the most recent version of the STOPP criteria to assess potentially inappropriate prescribing. Using two different approaches (unpaired and paired samples), we obtained consistent conclusions. However, owing to the secondary nature of this analysis, 35 (44%) of 80 STOPP criteria for which relevant patient information was unavailable could not be applied (see appendix 1). Like other explicit measures of potentially inappropriate prescribing, STOPP does not account for clinical judgment and individual clinical circumstances in which prescribing may be justified and appropriate in certain patients. However, STOPP has consistently been associated with poorer patient outcomes.[13] The quality of clinical coding of diagnoses was somewhat variable, which precluded application of the START criteria to identify prescribing omissions. This may be of

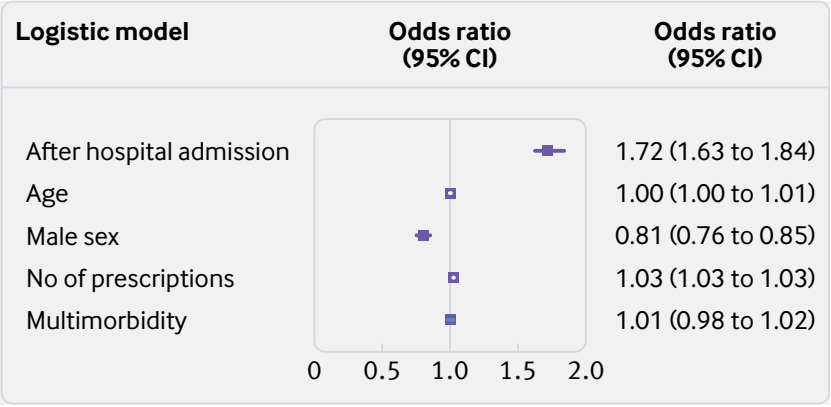

Fig 2 | Estimated odds ratios (with 95% credible intervals) for presence of potentially inappropriate prescribing among only participants admitted to hospital. Reference groups were before hospital admission and female sex. Also adjusted for patient health cover type, which did not show any significant association

particular interest for future research assessing the effect of hospital admission on appropriateness of prescribing, as unintentional omission of treatments is noted as the most common medication error at transitions of care.[37]

We addressed the quality of clinical and diagnostic coding by doing a sensitivity analysis using a prescription based measure of multimorbidity for adjustment and showed little effect on the results. Although general practices were recruited from a wide geographical area, they may not be representative of all practices, with the potential for volunteer bias. However, the analysis included patients with any type of health cover, compared with other studies limited to participants eligible for the means tested GMS scheme. Variability in coding for hospital admission existed between practices, and private hospital admissions were not captured, leading to potential for misclassification of exposure status for patients. However, the vast majority of secondary care interactions for older patients would be with public hospitals, so this is unlikely to significantly affect the findings. A high percentage of patients had complete follow-up over the course of the study. We did not have access to reasons for loss to follow-up, which could include mortality, moving practice, or admission to care homes (residential or nursing). However, results were robust to the possibility of dependent censoring. Although we adjusted for a range of characteristics of patients, as with any observational study potential exists for unmeasured confounding, which may partly or fully explain the relation between hospital admission and potentially inappropriate prescribing. We assessed the robustness of our result to different adjustment methods by using a propensity matched sensitivity analysis, but residual confounding due to other factors, such as the severity of illness, may still exist.

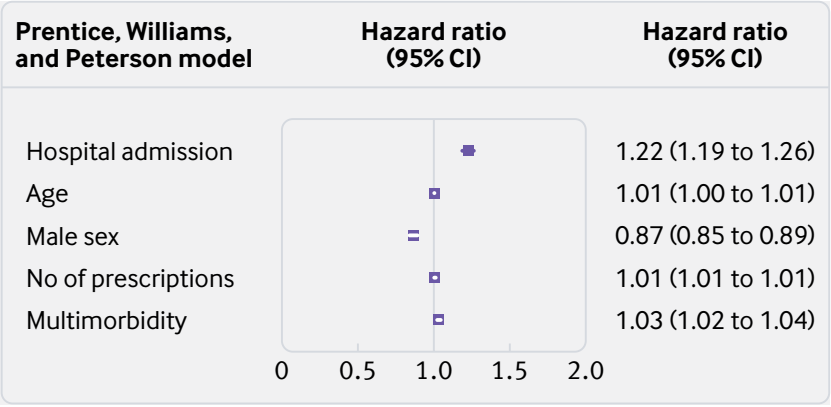

Fig 3 | Estimated hazard ratios (95% CI) for rate of distinct potentially inappropriate prescribing events among propensity score matched participants. Reference groups were no hospital admission and female sex

Comparison with previous studies

The literature examining the effect of hospital admission on potentially inappropriate prescribing is limited. Some studies have compared medication appropriateness at hospital admission and discharge, including potentially inappropriate prescribing defined by Beers criteria alone or in addition to STOPP/START.[38-40] In these studies, either no difference or a small reduction in potentially inappropriate prescribing was found between admission and discharge.[38-40] However, only the relatively short period of hospital admission was considered and the effect on primary care prescribing after discharge was not assessed. These studies included between approximately 180 and 2000 patients; in contrast to our study of more than 40 000 people, they may have been underpowered to detect an association.

A previous study assessed the prevalence of potentially inappropriate prescribing among 1016 older GMS scheme patients in Ireland presenting at one emergency department after a fall.[41] The overall prevalence of both the STOPP criteria (version 1) and Beers criteria (2012) did not change in the 12 months after the fall compared with before the fall. Prescribing of some drugs associated with falls, such as neuroleptics and benzodiazepines, did decrease, however. Discordance between these findings and ours may be because these patients were attending hospital for a specific adverse event (a fall), so an assessment of risk factors contributing to this, including drugs, was likely done during or after discharge from hospital.

In our study, we applied the recently revised 2015 STOPP 2 criteria—that is, the most current definition of potentially inappropriate prescribing. The prevalence here is closely comparable to estimates from other studies using STOPP 2, which ranged from 40.4% and 56% among community dwelling people aged at least 65 and 80 years, respectively,[42 43] to between 41.5% and 71.5% in older patients being discharged from hospital.[39 44] As in our study, long term prescription of benzodiazepines and Z drugs was common in several other studies using STOPP 2.[39 42-45] In contrast, the long term use of proton pump inhibitors, the most common criterion in our study, was noted as particularly prevalent in only two previous studies using STOPP 2.[39 45]

Table 2 | Comparison of models adjusted for morbidity using Charlson comorbidity index (standard analysis) and RxRisk (sensitivity analysis)

Estimate	No	Hazard ratio (95% confidence interval)*	Odds ratio (95% credible interval)*
Admitted to hospital (relative to not admitted)			
Adjusted for Charlson comorbidity index	28 831	1.24 (1.20 to 1.27)	1.49 (1.42 to 1.59)
Adjusted for RxRisk	38 169	1.25 (1.22 to 1.29)	1.55 (1.47 to 1.64)
After admission (relative to before admission)			
Adjusted for Charlson comorbidity index	9549	-	1.72 (1.63 to 1.84)
Adjusted for RxRisk	11 277	-	1.71 (1.63 to 1.81)

*Additionally adjusted for age, sex, number of prescriptions items, and health cover type.

Implications for clinicians, research, and policy

Inpatient admissions can provide the opportunity for specialist teams to review and optimise management of older patients' chronic conditions, including their drugs.[46] Although hospital admissions have the potential to improve management of drugs, this study suggests these possible benefits to appropriateness of prescribing after discharge to primary care are not being realised. Our findings suggest that hospital admission (which may result from a change in a patient's clinical status and may result in an intensification of healthcare) is an important driver of potentially inappropriate prescribing and the overuse and/or misuse of drugs. Medicines management services for inpatients in Ireland are broadly similar to those in the UK; however, the extent to which they are provided in practice is variable owing to resourcing of hospital pharmacy services. In approximately 40% of Irish hospitals, pharmacists do admission medication reconciliation and review, which is similar to the proportion in UK hospitals, although fewer Irish hospitals involve pharmacists in emergency department and acute medical assessment units.[47] Most provide inpatient clinical pharmacy services; however, unlike the UK, in most (86%) Irish hospitals pharmacists had no formal involvement in the discharge prescribing process. The vast majority also do not supply drugs to patients on discharge, and about half provide pharmacist counselling on discharge drugs.[47] The 2017 National Patient Experience Survey report underlines the need for improved medication management services at discharge, where 40% of patients reported not being advised about drug side effects to be aware of.[48]

Poor coordination of transitions between care settings (from secondary to primary care), can put patients at increased risk of medication errors, adverse drug events, and readmissions.[49-51] Improving coordination of care, particularly for older patients with complex care needs, has been identified as an international policy priority.[52 53] Transitional care interventions for older patients with chronic disease discharged from hospital to primary care have been evaluated in a recent systematic review.[54] Evidence suggests that these interventions can reduce mortality, hospital readmissions, and number of readmission days after 3-18 months (for example, a mortality risk difference at 18 months of −0.07 (95% confidence interval −0.12 to −0.02)), but no evidence of a benefit to quality of life was shown in meta-analysis.[54] A recent quasi-experimental study evaluated the effect of a medication management system (Pharm2Pharm) provided by hospital and community pharmacists for older adults at risk of medication problems.[55] The intervention seemed to reduce the drug related hospital admission rate and provide cost savings.

More effective means of medicines reconciliation in hospital and primary care—for example, through the availability of a summary care record—may allow for more of clinicians' time to be focused on assessment of the appropriateness of drugs.[56] Similarly, implementing a standardised electronic format for discharge summaries could improve their quality and reduce discrepancies arising from transitions between hospital and primary care.[57] As well as reducing deficits in communication, a robust electronic record system could also incorporate decision support to aid clinicians in reviewing prescriptions, which, combined with incentives and professional education, has been shown to effectively reduce high risk prescribing and associated adverse events.[58] A large scale study of almost a million patients in UK general practice showed high variation between practices in the prevalence of such high risk prescribing,[59] suggesting that practice level interventions to improve prescribing should be targeted. Variation among practices in the effect of hospital admission on appropriate prescribing also warrants examination to help to inform strategies to improve this.

Individual clinicians may consider several potential solutions. A recent systematic review identified incomplete clinical picture (information deficits due to poor communication among multiple prescribers and fragmentation at care interfaces) as a barrier to minimising inappropriate drugs by prescribers.[60] Many of the common STOPP criteria in our study relate to inappropriate duration of use, so documenting and clearly communicating the intended duration of the prescription or a planned review date would ensure that other clinicians such as general practitioners have complete information for reviewing and stopping such prescriptions. Similarly, documentation of the indication for a drug will facilitate review of appropriateness and continued need.[60] The indication and duration should also be discussed with patients, which would mean that they expect future review or stopping of drugs and thus reduce the ambivalence/resistance of patients to change as a barrier to appropriate prescribing.[60 61] Prescribers have also cited a lack of evidence and difficulty in assessing the benefits/harms of treatment

as a barrier.[60] Several evidence based guidelines have recently been developed to support decisions on deprescribing specific drugs, including proton pump inhibitors, benzodiazepines, and Z drugs, which were among the most prevalent problems identified in our study.[62 63] Deprescribing algorithms and patient information leaflets and decision aids as companions to these guidelines are also available from www.deprescribing.org.

We cannot determine whether the observed increase in potentially inappropriate prescribing is a consequence of illness that prompted hospital admission, and the increased complexity this may bring, or whether potentially inappropriate prescribing is a consequence of further medical intervention during the hospital stay. Future research should identify the mechanisms by which hospital admission is associated with potentially inappropriate prescribing, including detailed review of patients' clinical records to explore how potentially inappropriate prescribing may have been contributory or causal in hospital admissions and to understand the clinical decisions (in both primary and secondary care) that resulted in potentially inappropriate prescribing among patients after discharge from hospital. Research should also evaluate how to overcome these problems to enhance appropriateness of prescribing for older patients after discharge. This may include better continuity of information through improved health information and communication technology infrastructure, as well as formal transitional care programmes.[54 64] In addition, hospital based interventions to enhance appropriateness of prescribing for older patients should be evaluated, such as reviews using prescribing criteria like STOPP or alignment of clinical pharmacists with medical teams to provide integrated medicines management.[65 66]

Conclusions

This study shows that potentially inappropriate prescribing is becoming increasingly prevalent among community dwelling older people according to the most recent STOPP criteria. Furthermore, hospital admission is independently associated with an increased risk of potentially inappropriate prescribing after discharge back to primary care. Identifying optimal management strategies for older people is vital to ensure that the risk of inappropriate drugs is minimised after transitions of care.

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Data sharing: No additional data available.

Transparency statement: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Appendix 1-6

Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care

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ABSTRACT

OBJECTIVE

To investigate the associations between direct oral anticoagulants (DOACs) and risks of bleeding, ischaemic stroke, venous thromboembolism, and all cause mortality compared with warfarin.

DESIGN

Prospective open cohort study.

SETTING

UK general practices contributing to QResearch or Clinical Practice Research Datalink.

PARTICIPANTS

132 231 warfarin, 7744 dabigatran, 37 863 rivaroxaban, and 18 223 apixaban users without anticoagulant prescriptions for 12 months before study entry, subgrouped into 103 270 patients with atrial fibrillation and 92 791 without atrial fibrillation between 2011 and 2016.

MAIN OUTCOME MEASURES

Major bleeding leading to hospital admission or death. Specific sites of bleeding and all cause mortality were also studied.

RESULTS

In patients with atrial fibrillation, compared with warfarin, apixaban was associated with a decreased risk of major bleeding (adjusted hazard ratio 0.66, 95% confidence interval 0.54 to 0.79) and intracranial bleeding (0.40, 0.25 to 0.64); dabigatran was associated with a decreased risk of intracranial bleeding (0.45, 0.26 to 0.77). An increased risk of all cause mortality was observed in patients taking rivaroxaban (1.19, 1.09 to 1.29) or on lower doses of apixaban (1.27, 1.12 to 1.45).

In patients without atrial fibrillation, compared with warfarin, apixaban was associated with a decreased risk of major bleeding (0.60, 0.46 to 0.79), any gastrointestinal bleeding (0.55, 0.37 to 0.83), and upper gastrointestinal bleeding (0.55, 0.36 to 0.83); rivaroxaban was associated with a decreased risk of intracranial bleeding (0.54, 0.35 to 0.82). Increased risk of all cause mortality was observed in patients taking rivaroxaban (1.51, 1.38 to 1.66) and those on lower doses of apixaban (1.34, 1.13 to 1.58).

CONCLUSIONS

Overall, apixaban was found to be the safest drug, with reduced risks of major, intracranial, and gastrointestinal bleeding compared with warfarin. Rivaroxaban and low dose apixaban were, however, associated with increased risks of all cause mortality compared with warfarin.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Randomised controlled trials of anticoagulants have shown the non-inferiority of direct oral anticoagulants (DOACs) compared with warfarin

Observational studies of anticoagulants, investigating outcomes in more real world environments, have mostly studied patients with atrial fibrillation

Studies including patients without atrial fibrillation have either predated the increase in use of DOACs, or have had incomplete patient selection or other study design weaknesses

WHAT THIS STUDY ADDS

Apixaban is associated with a decreased risk of major bleeding events in patients with atrial fibrillation and without atrial fibrillation compared with warfarin

Rivaroxaban is associated with a decreased risk of intracranial bleeds in patients without atrial fibrillation compared with warfarin

Rivaroxaban and low dose apixaban are associated with an increased risk of all cause mortality in patients with atrial fibrillation and without atrial fibrillation compared to warfarin

Introduction

Anticoagulants are used for the prevention and treatment of venous thromboembolism and to reduce the risk of stroke in patients with either atrial fibrillation or after acute pulmonary embolism, deep vein thrombosis, or hip or knee replacement surgery.[1-4] Warfarin has been used for six decades but in the last eight years its use has been gradually replaced by a new class of direct acting oral anticoagulants (DOACs) including dabigatran, rivaroxaban, and apixaban. Unlike warfarin, these drugs have set doses and do not generally require regular international normalisation ratio blood test monitoring.[5] They also have faster onset and offset of action. There are, however, some concerns regarding the safety of DOACs with respect to bleeding because there is an absence of or a limited choice of antidotes, some of which are also expensive.[6 7]

Atrial fibrillation is the most common condition requiring anticoagulants, and most clinical trial evidence has been based on this group of patients. These trials have established non-inferiority in the anticoagulating qualities of DOACs compared with warfarin in controlled trial settings,[8-10] but there are residual concerns regarding their safety, particularly in more real world settings, where they are prescribed to a broad range of patients. A recent meta-analysis has shown that apixaban has advantages over warfarin, providing a better balance between efficacy and safety.[11] The included studies were differently designed, and none provided data for all DOACs. These findings, therefore, represent only indirect comparisons between different types of DOACs, derived using network meta-analysis techniques.

Most well powered observational studies have also focused on patients with atrial fibrillation.[12-25] Only two have provided data for the wider population,[13 15]

and only one of these presented results for the group without atrial fibrillation.[13] Both studies were based on data from commercially insured patients, containing billing information, and were conducted a few years ago, when warfarin was more commonly prescribed. Our study aims, for all incident users of anticoagulants, to compare the risks (major bleeding and mortality) and benefits (reduced ischaemic stroke and venous thromboembolism) associated with the three commonest types of DOACs compared with warfarin. We provide separate results for the group with atrial fibrillation and for the group prescribed the drugs because of other conditions.

Methods

Data sources

We used two UK primary care databases QResearch and Clinical Practice Research Datalink (CPRD). Each is representative of the national population in terms of the number of practices and of patients that contribute.[26] Both have been widely validated against other sources of information and used in a wide range of clinical studies.[27] All 1457 QResearch (version 42) and 357 CPRD (November 2016) practices were linked at the patient level to hospital admissions data, which provided dates and diagnoses for hospital stays.[28] These practices were also linked to mortality data supplied by the Office for National Statistics, which include diagnoses and dates of death. Most patients in linked practices also had information on their level of deprivation based on quintiles of Townsend score and provided by Census 2011.[29] We used READ codes to extract the information from general practices and ICD-10 (international classification of diseases, 10th revision) codes for Hospital Episode Statistics and Office for National Statistics data (see supplementary table 1).

Study design

We used a new-user design to capture all events occurring after starting treatment and to reduce the impact of confounding.[30] For a study period from January 2011 to the latest date of Hospital Episode Statistics linked data (October 2016 for QResearch and March 2016 for CPRD), patients prescribed the oral anticoagulants warfarin, dabigatran, rivaroxaban, and apixaban, and aged from 21 to 99 at study entry date, formed the cohort. The entry date was defined as the date of the first prescription of any of the anticoagulant drugs. To facilitate a direct comparison between new users of direct oral anticoagulants (DOACs) against new users of warfarin, and to reduce the impact of indication bias, patients were excluded if they had any anticoagulant prescription in the last 12 months before the entry date. To ensure the quality of data, patients were also excluded if they had either fewer than 12 months of records before entry or had no valid Townsend score.

Patients were followed from their first prescription of an anticoagulant until they experienced an outcome of interest or were censored. Patients were censored when: they stopped or suspended treatment (at 30 days after the expected end date of any prescription, where the gap between the expected prescription end date and the start date of any subsequent prescription was more than 30 days); they switched treatment (at the day before the prescription start for a different anticoagulant); they left a practice (at the day of deregistration); they died; or the study period ended. For the analyses of dosages, we also censored patients when they changed to a different dose.

Outcomes

To assess the scale of unintended adverse events of anticoagulant treatment, the primary outcome was major bleeding after entry to the study which led to a hospital admission or death, based on linked hospital or mortality records. The first occurrence was used in the analyses of specific outcomes including intracranial bleed, haematuria, haemoptysis, and gastrointestinal bleed (also separated into upper and lower, where recorded), because these were identified as possibly preventable and potentially life threatening or life changing.

To assess the efficacy of anticoagulant treatments, the following secondary outcomes were considered: ischaemic stroke, venous thromboembolism, and all cause mortality. The outcome date was the earliest record after entry to the study from GP, hospital, and mortality data records. These analyses were focused on primary prevention so patients having venous thromboembolism events before entry to the study were excluded from the analysis of the risk of venous thromboembolism. Similarly, patients with previous ischaemic strokes were excluded from the analysis of the risk of ischaemic stroke.

Exposure to anticoagulants

Three DOACs – dabigatran, rivaroxaban, and apixaban – were compared with warfarin. Edoxaban was not included because it was licensed in the UK at the end of 2015. Acenocoumarol and phenindione were not included because they have been rarely prescribed in the UK.

Extracted data for anticoagulant prescriptions contained the preparation details, number of days, and number of tablets per day. The daily dose was averaged for each prescription and categorised as lower or higher than the recommended daily dose: 300 mg for dabigatran, 20 mg for rivaroxaban, and 10 mg for apixaban. In the subcohort with atrial fibrillation, higher dose corresponds to standard dose. Precise dosages for warfarin were not available because they vary according to international normalisation ratio measurement and are not consistently recorded in general practice.

Confounding factors

It is possible that patients at higher risk of bleeding may preferentially be prescribed DOACs rather than warfarin, so all analyses were adjusted for demographic and clinical variables, either because

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they may have been used as indicators for prescribing a specific anticoagulant or because they have possible associations with increased risk of bleeding, ischaemic stroke, or venous thromboembolism. We similarly adjusted for comorbidities, previous events, and drugs also used as indicators or associated with increased risks.[31] The covariates were assessed at the date when the anticoagulant was first prescribed.

Demographic and lifestyle variables, included because they affect the risk of bleeding, ischaemic stroke, or venous thromboembolism, were: sex; age at entry to the study;[32] self assigned ethnicity; smoking status; alcohol use;[33] and deprivation.[32 34] Body mass index and systolic blood pressure were included for the same reason.

Comorbidities included if recorded before the drug start were: alcohol dependence; bleeding disorders; cancer (the 12 most commonly occurring types); chronic liver disease or pancreatitis;[33] chronic obstructive pulmonary disease; chronic renal disease;[33] congestive cardiac failure; coronary heart disease; diabetes; dyspepsia or heartburn; treated hypertension;[33] previous ischaemic stroke or transient ischaemic attack; oesophageal varices; peptic ulcer; valvular heart disease; venous thromboembolism; and previous bleed (including intracranial, haematuria, haemoptysis, or gastrointestinal). If recorded in the six months before the start of anticoagulant treatment, falls or hip fractures and hip or knee replacement operations were both included in the analysis.

Recent and concurrent drug use, included in the analysis because they may affect the risk of bleeding or interact with anticoagulants, were: proton pump inhibitors; macrolide antibiotics; antiplatelets;[33] antidepressants;[35] anticonvulsants (phenytoin or carbamazepine); non-steroidal anti-inflammatory drugs; corticosteroids; and statins. For women, hormonal treatments, which included hormone replacement therapy and oral contraceptives, were also added to the analysis of venous thromboembolism outcome because they may increase the risk of venous thromboembolism.

Finally, year of entry to the study was included as a confounder both because of changes in recorded rates of outcomes over the study period and because the balance of prescribing between the different anticoagulants was also changing. Specifically, rates of bleeding, ischaemic stroke, and venous thromboembolism were changing in the general population and, while at the beginning of the study warfarin was overwhelmingly the most common anticoagulant prescription, by the end of the study combined prescription rates for DOACs were considerably higher than for warfarin.

Statistical analysis

The baseline characteristics for each group of patients and anticoagulant of interest were described as percentages, means (SD), or medians (interquartile ranges). Incidence rates for each outcome were calculated based on the numbers with the outcome and the person years of follow-up, and were age and sex standardised for each drug. To estimate the risks associated with each DOAC, an outcome specific Cox model containing all confounding factors was used, with warfarin as a primary reference. To quantify differences between apixaban and other DOACs an additional analysis was run with apixaban as a reference.

To account for a log-normal distribution, logarithm of body mass index was used. Age was included using fractional polynomials. Patients with missing ethnicity data were included in the white category. To assess the validity of this assumption, a sensitivity analysis was run for ethnicity where the missing values were included as a separate category. Missing values for body mass index, smoking status, alcohol consumption, and systolic blood pressure were assumed as missing at random and imputed using chained equations.[36] We used an outcome specific imputation model including outcome, length of follow-up, all confounders, anticoagulant type, and prescribed dose. Where possible, depending on numbers, we pooled the results obtained from QResearch and CPRD using a fixed effect model with inverse variance weights. Where any heterogeneity was detected, the results were combined using a random effect model.[37] Because the CPRD sample was relatively small, not every outcome in the more disaggregated analyses yielded a sufficient number of events. This mainly occurred for the subcohort of patients without atrial fibrillation and in the dosage analyses. In these cases, results from QResearch alone were reported.

We carried out analyses for the cohort of all patients who started anticoagulants in the study period, with additional separate analyses for a subcohort with atrial fibrillation and the remaining subcohort with other indications for anticoagulant prescription. The main results presented are those for the two subcohorts separately, with the findings for the pooled cohort presented as supplementary material.

To estimate the absolute magnitude of risks associated with different DOACs when compared with warfarin, we calculated numbers needed to treat or harm using the adjusted hazard ratios and baseline rates for warfarin.[38] Baseline rates were estimated by weighting rates from QResearch and CPRD. We calculated the numbers for 6, 12, 18, and 24 months after treatment commenced.

In addition to the sensitivity analysis for ethnicity described previously, three further sensitivity analyses were run. Being admitted to hospital for bleeding, ischaemic stroke, or venous thromboembolism may result in a switch of anticoagulant used without any subsequent GP records of the change. So patients who were admitted to hospital for one of these outcomes were censored at the time of the hospital stay in the analysis of other outcomes in a second sensitivity analysis. To assess the validity of the assumption that missing data were missing at random, a third sensitivity analysis was run only on patients with complete data.

The fourth sensitivity analysis, using propensity score weighting,[39] was run on the subcohort with

complete data. This approach has been used previously for studying DOACs in comparison with warfarin.[40] Three separate propensity scores were developed. The first to predict the use of dabigatran among dabigatran and warfarin users. The second to predict use of rivaroxaban among rivaroxaban and warfarin users. The third to predict use of apixaban among apixaban and warfarin users. All available variables described as confounding factors were included in the development of the propensity scores. Patients with propensity scores from non-overlapping regions were excluded from the relevant analysis. Three separate Cox models were then run, where the use of each DOAC in turn was adjusted for the relevant propensity score.

Patient involvement

Patient representatives from the QResearch Advisory Board wrote the information for patients on the QResearch website about the use of the database for research. Patients were not involved in setting the research question, the outcome measures, the design, or implementation of this study. Lay people and patient representatives were involved in writing and approving the lay summaries during the bid process. The patient representative in the publication review process expressed appreciation of the real world nature of the study, highlighting the usefulness of such studies for informing doctor-patient discussions.

Results

Cohort characteristics

Figure 1 shows that 156 005 patients from QResearch and 40 056 from Clinical Practice Research Datalink (CPRD), who started or restarted anticoagulants (after more than a 12 month gap) between 2011 and 2016, were eligible for inclusion. Overall, 53% were diagnosed with atrial fibrillation (81 251 in QResearch and 22 019 in CPRD) leaving 47% of patients prescribed anticoagulants for other indications (74 754 in QResearch and 18 037 in CPRD).

In the subcohort with atrial fibrillation, across the databases, there were 70 585 (68%) patients taking warfarin, 5537 (5%) taking dabigatran, 16 547 (16%) taking rivaroxaban, and 10 601 (10%) taking apixaban. In the subcohort without atrial fibrillation, there were 61 646 (66%) taking warfarin, 2207 (2%) taking dabigatran, 21 316 (23%) taking rivaroxaban, and 7622 (8%) taking apixaban. Figure 2 and supplementary

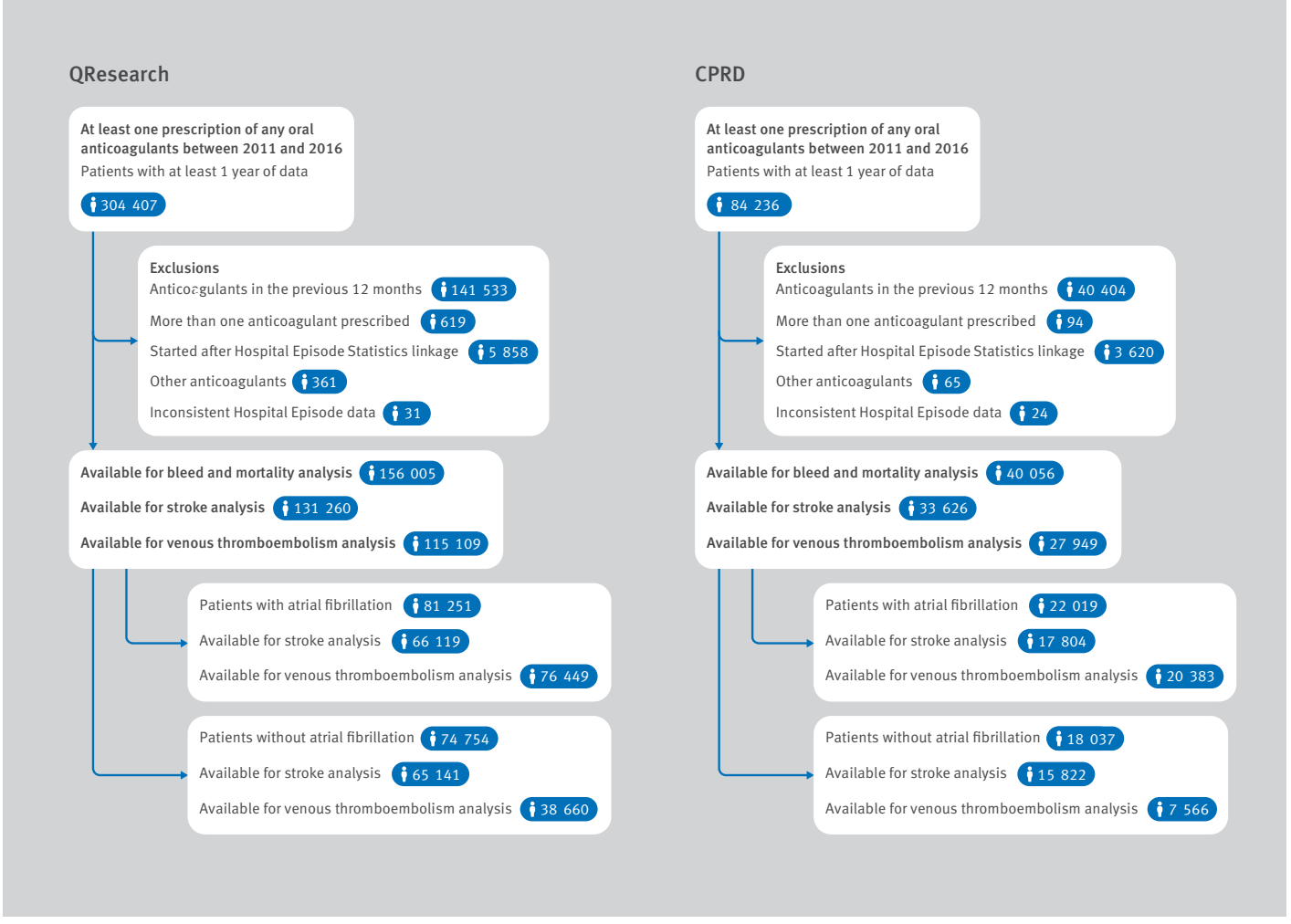

Fig 1 | Flow of the included patients for QResearch and Clinical Practice Research Datalink (CPRD) analysis

table 2 show that although overall 67% of patients were prescribed warfarin, its use declined during the study period over both databases from 98% in 2011 to 23% in 2016. DOAC use had risen, from 1% to 42% for rivaroxaban and from 0% to 31% for apixaban. Dabigatran reached a peak in 2013 (10%) but dropped to 3% in 2016. This pattern was similar for patients with atrial fibrillation and without atrial fibrillation.

Table 1 and supplementary table 3 show the characteristics of patients with atrial fibrillation by database. Table 2 and supplementary table 4 show the characteristics of patients without atrial fibrillation by database. The tables show the consistency between the cohorts from the two databases apart from the slightly shorter exposure period in CPRD because of the shorter study inclusion period. Patients were exposed to warfarin for longer than to direct oral anticoagulants (DOACs) in both subcohorts, with a median exposure of 11 months in QResearch (9 months in CPRD) for the atrial fibrillation subcohort and six months (in both databases) for the subcohort without atrial fibrillation. In comparison, the DOACs had median duration of nine months in QResearch (five months in CPRD) for the atrial fibrillation subcohort, and three months in both QResearch and CPRD for the subcohort without atrial fibrillation.

Table 1 and table 2 show that across both databases, patients with atrial fibrillation were older than patients without atrial fibrillation (mean age 75 *v* 66), had more age related comorbidities, and used more related drugs. More patients in the subcohort with atrial fibrillation than in the subcohort without atrial fibrillation had heart related diseases such as congestive cardiac failure (13% *v* 7%), coronary heart disease (25% *v* 17%), treated hypertension (62% *v* 42%), diabetes (19% *v* 15%), and previous ischaemic stroke (19% *v* 13%); a much lower proportion had venous thromboembolism (6% *v* 50%). The proportion of patients diagnosed with cancer, was slightly higher in the subcohort without atrial fibrillation (13.4%) than in the subcohort with atrial fibrillation (12.4%) in both databases.

In the subcohort with atrial fibrillation, patients prescribed different anticoagulants were of similar age (with means ranging between 74.4 and 76.6), but in the subcohort without atrial fibrillation, patients on warfarin were the youngest (overall mean 66.5) and patients on apixaban were the oldest (overall mean 74.0). Across both databases and both subcohorts, the proportion of patients with chronic renal disease was highest in the warfarin group (2.9%) and among the patients using DOACs was highest in the apixaban groups (on average 2.2%). Proportions of patients in the different ethnic, smoking status, and alcohol consumption categories, and quintiles of Townsend deprivation scores were broadly similar across subcohorts, types of anticoagulants, and databases (see supplementary tables 3 and 4).

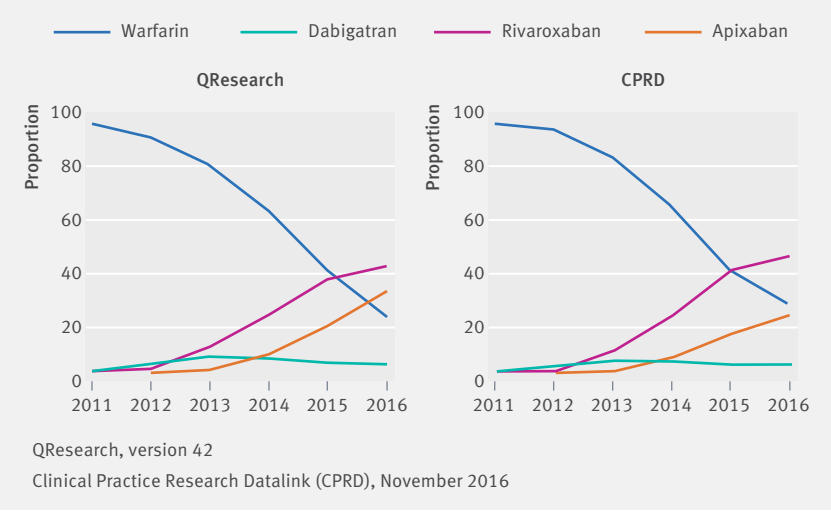

Fig 2 | Proportion of patients prescribed different anticoagulants in each year by database

Incidence rates

Table 3 and table 4 show follow-up time and the number of events for subcohorts with and without atrial fibrillation respectively. Supplementary table 5 shows the data for all patients. The rates of major bleeding in the warfarin groups varied between 25.1 and 35.2 per 1000 person years. In warfarin users, the rates for gastrointestinal bleeding were higher in CPRD in both subcohorts.

In the subcohort without atrial fibrillation, the rates of different bleeds were generally slightly lower in QResearch than CPRD, although the number of events were too low for comparison. In the subcohort without atrial fibrillation in both QResearch and CPRD, the highest rates of venous thromboembolism were in patients taking rivaroxaban (180 and 240 per 1000 person years, respectively).

Table 3 and table 4 show that the mortality rates were consistently higher in patients without atrial fibrillation (from 58 to 87 per 1000 person years in QResearch and from 57 to 108 in CPRD) than in patients with atrial fibrillation (43 to 55 in QResearch and 42 to 62 in CPRD).

Overall, there was good consistency between the databases. For 120 combinations of subgroup, outcome, and drug, there were only eight combinations where rate pairs differed by more than 1 per 100 person years.

Associations with anticoagulant exposure

Figure 3 shows the results for patients with atrial fibrillation and figure 4 shows the results for patients without atrial fibrillation, with reference to warfarin. Figure 5 shows the results for both groups with reference to apixaban. Supplementary tables 5-7 show the adjusted hazard ratios in each of the two databases. Hazard ratios were adjusted for age, sex, ethnicity, smoking, alcohol, Townsend quintile, body mass index, systolic blood pressure, falls and hip fracture, hip or knee operations, comorbidities (alcoholism, atrial fibrillation, treated hypertension, chronic kidney disease, chronic obstructive pulmonary disease,

Table 1 | Patients with atrial fibrillation: selected baseline characteristics of patients and comorbidities in the QResearch and Clinical Practice Research Datalink (CPRD) cohorts. Values are percentages (numbers) unless stated otherwise

	QResearch				CPRD			
Characteristic	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Total no of patients	53 921	4534	13 597	9199	16 664	1003	2950	1402
Median (interquartile range) days of treatment	344 (150-714)	271 (89-627)	265 (97-496)	248 (100-440)	286 (135-589)	214 (87-479)	163 (69-328)	143 (60-295)
Sex:								
Men	55.5 (29 913)	58.0 (2629)	54.4 (7391)	51.8 (4764)	55.7 (9278)	61.5 (617)	54.1 (1596)	54.9 (769)
Women	44.5 (24 008)	42.0 (1905)	45.6 (6206)	48.2 (4435)	44.3 (7386)	38.5 (386)	45.9 (1354)	45.1 (633)
Mean (SD) age at baseline	74.8 (10.4)	74.7 (10.7)	75.8 (10.9)	76.5 (10.9)	74.8 (10.3)	74.4 (10.8)	75.9 (10.8)	76.6 (10.9)
Comorbidities at baseline:								
Alcohol dependence	2.4 (1285)	3.2 (143)	2.9 (388)	3.1 (286)	2.2 (365)	2.9 (29)	2.8 (83)	3.4 (48)
Bleeding disorders	0.9 (486)	0.8 (38)	1.0 (136)	1.1 (102)	1.2 (193)	1.0 (10)	1.5 (43)	1.4 (20)
Cancer (any)	12.1 (6530)	12.5 (567)	13.3 (1806)	13.1 (1205)	12.4 (2073)	11.2 (112)	12.9 (382)	12.8 (179)
Chronic liver disease or pancreatitis	1.1 (582)	1.4 (62)	1.4 (187)	1.3 (120)	0.9 (155)	1.7 (17)	1.6 (46)	0.9 (13)
Chronic obstructive pulmonary disease	9.9 (5355)	8.4 (382)	9.7 (1314)	10.0 (920)	9.5 (1586)	9.6 (96)	9.7 (287)	8.1 (114)
Chronic renal disease	2.8 (1487)	1.0 (45)	1.6 (224)	2.1 (195)	2.9 (483)	1.5 (15)	2.0 (60)	1.9 (27)
Congestive cardiac failure	14.1 (7595)	11.1 (502)	11.4 (1553)	12.8 (1173)	13.4 (2227)	11.1 (111)	11.0 (324)	14.9 (209)
Coronary heart disease	25.3 (13 625)	22.0 (997)	22.1 (3005)	24.3 (2234)	25.5 (4251)	23.0 (231)	21.1 (622)	25.1 (352)
Diabetes	19.0 (10 255)	17.3 (784)	17.9 (2435)	19.3 (1772)	17.9 (2979)	16.7 (167)	18.0 (530)	19.0 (267)
Dyspepsia	18.0 (9684)	18.0 (817)	18.6 (2523)	19.1 (1759)	26.1 (4355)	25.4 (255)	26.9 (795)	24.8 (348)
Falls or hip fracture*	7.6 (4124)	7.1 (322)	7.5 (1015)	8.2 (756)	6.0 (992)	4.9 (49)	6.7 (199)	6.6 (92)
Hip or knee operation*	0.6 (319)	0.9 (40)	1.0 (131)	0.6 (59)	1.5 (246)	1.2 (12)	1.7 (51)	1.8 (25)
Hypertension	62.2 (33 555)	60.6 (2746)	59.2 (8053)	59.9 (5513)	62.3 (10 383)	59.9 (601)	62.1 (1833)	62.8 (881)
Ischaemic stroke†	18.1 (9752)	22.0 (999)	16.8 (2290)	22.7 (2091)	18.0 (3001)	23.5 (236)	19.7 (582)	28.2 (396)
Oesophageal varices	0.1 (51)	0.1 (6)	0.1 (11)	0.1 (11)	0.1 (9)	NA	NA	NA
Peptic ulcer	7.5 (4065)	7.4 (336)	7.1 (971)	8.4 (772)	8.3 (1380)	7.9 (79)	8.8 (260)	9.6 (135)
Valvular heart disease	12.2 (6553)	9.4 (428)	8.8 (1191)	10.6 (975)	9.8 (1630)	7.2 (72)	6.6 (196)	9.1 (127)
Venous thromboembolism†	6.4 (3450)	3.0 (138)	6.1 (830)	4.2 (384)	7.7 (1280)	5.6 (56)	7.3 (216)	6.0 (84)
Previous bleed:								
Any†	23.8 (12 848)	25.9 (1176)	26.0 (3541)	27.1 (2493)	28.0 (4674)	29.5 (296)	29.5 (869)	29.7 (417)
Intracranial†	0.8 (435)	1.2 (54)	1.1 (146)	1.6 (143)	1.1 (191)	1.9 (19)	1.4 (41)	2.1 (30)
Haematuria	10.9 (5883)	12.9 (583)	12.2 (1665)	12.1 (1110)	12.1 (2018)	12.0 (120)	12.0 (354)	11.4 (160)
Haemoptysis†	2.6 (1428)	2.3 (106)	2.7 (364)	2.7 (247)	3.6 (599)	3.4 (34)	3.3 (97)	3.2 (45)
Previous gastrointestinal bleed:†								
All	12.6 (6785)	13.6 (615)	13.8 (1878)	14.8 (1360)	15.7 (2610)	16.7 (168)	17.1 (504)	18.3 (256)
Upper	4.2 (2260)	4.5 (203)	4.7 (640)	5.1 (471)	5.1 (844)	5.1 (51)	6.2 (184)	6.0 (84)
Lower	9.4 (5067)	10.4 (472)	10.3 (1394)	10.9 (1004)	12.0 (2004)	12.8 (128)	12.9 (381)	14.0 (196)
Other drugs:								
Proton pump inhibitors	43.4 (23 375)	44.1 (2000)	41.1 (5593)	44.1 (4053)	41.4 (6894)	41.3 (414)	42.1 (1243)	42.4 (594)
Antibiotics‡	10.1 (5460)	8.7 (396)	7.5 (1015)	6.8 (622)	9.0 (1495)	6.9 (69)	7.8 (231)	5.1 (71)
Antiplatelet	29.9 (16 135)	23.3 (1055)	19.8 (2694)	17.4 (1602)	40.2 (6705)	39.1 (392)	31.0 (914)	33.5 (469)
Antidepressants	15.7 (8444)	14.8 (669)	15.4 (2095)	16.8 (1550)	14.5 (2420)	12.9 (129)	17.3 (510)	17.1 (240)
Anticonvulsants	0.8 (413)	0.4 (20)	0.6 (85)	0.8 (69)	0.8 (126)	0.5 (5)	0.9 (26)	0.9 (12)
NSAIDs	6.9 (3709)	8.5 (386)	7.3 (994)	5.7 (523)	6.6 (1105)	8.3 (83)	6.6 (195)	6.1 (85)
Corticosteroids	12.3 (6633)	11.2 (506)	10.7 (1450)	9.9 (914)	10.9 (1824)	8.9 (89)	10.2 (300)	8.6 (120)
Statins	55.2 (29 763)	53.6 (2428)	51.3 (6972)	54.1 (4975)	53.4 (8904)	52.9 (531)	51.2 (1509)	56.0 (785)
Hormones (women)	1.5 (370)	2.3 (43)	1.5 (93)	1.3 (57)	2.7 (199)	2.1 (8)	3.0 (40)	2.8 (18)

For information on age distribution, ethnicity, smoking, alcohol consumption, and Townsend quintiles see supplementary table 3.
NA=not applicable, fewer than 5 observations; NSAIDs=non-steroidal anti-inflammatory drugs.
*Within the last 6 months.
†Based on general practice and Hospital Episode Statistics records.
‡Within the last 6 months before the drug start date.

liver disease, coronary heart disease, congestive cardiac failure, any cancer, or valvular peptic ulcer), previous events (bleed, venous thromboembolism, or ischaemic stroke), drugs at the baseline (macrolides, antiplatelets, anticonvulsant, corticosteroids, NSAIDs, statins, or hormones), and study year.

In patients with atrial fibrillation, apixaban was associated with a lower risk of major bleed than warfarin (adjusted hazard ratio 0.66, 95% confidence interval 0.54 to 0.79) (fig 3) and rivaroxaban (fig 5). Dabigatran (0.45, 0.26 to 0.77) and apixaban (0.40, 0.25 to 0.64) were associated with lower risks of

Table 2 | Patients without atrial fibrillation: selected baseline characteristics of patients and comorbidities in the QResearch and Clinical Practice Research Datalink (CPRD) cohorts. Values are percentages (numbers) unless stated otherwise

	QResearch				CPRD			
Characteristic	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Total no of patients	47 331	1868	18 423	7132	14 315	339	2893	490
Median (interquartile range) days of treatment	196 (111-138)	88 (58-244)	89 (51-196)	115 (58-215)	193 (114-308)	78 (57-240)	86 (45-183)	102 (51-228)
Sex:								
Men	53.6 (25 377)	53.1 (992)	48.8 (8985)	51.7 (3689)	53.2 (7615)	53.1 (180)	47.3 (1368)	50.2 (246)
Women	46.4 (21 954)	46.9 (876)	51.2 (9438)	48.3 (3443)	46.8 (6700)	46.9 (159)	52.7 (1525)	49.8 (244)
Mean (SD) age at baseline	66.5 (15.6)	71.6 (12.9)	68.2 (15.7)	73.9 (13.6)	66.3 (15.9)	71.6 (12.7)	66.9 (16.4)	74.7 (13.5)
Comorbidities at baseline:								
Alcohol dependence	3.1 (1469)	2.6 (49)	3.3 (599)	3.3 (236)	2.3 (333)	2.1 (7)	3.2 (94)	3.9 (19)
Bleeding disorders	1.4 (641)	0.7 (14)	1.2 (221)	1.0 (73)	1.6 (231)	NA	1.9 (54)	1.0 (5)
Cancer (any)	13.5 (6405)	10.8 (202)	13.1 (2408)	13.3 (949)	13.8 (1971)	12.1 (41)	13.7 (396)	13.9 (68)
Chronic liver disease or pancreatitis	1.5 (699)	1.1 (20)	1.2 (229)	1.4 (97)	1.6 (228)	NA	1.5 (43)	3.1 (15)
Chronic obstructive pulmonary disease	8.2 (3899)	7.8 (146)	7.9 (1457)	10.1 (719)	8.4 (1205)	4.1 (14)	8.4 (242)	8.8 (43)
Chronic renal disease	3.1 (1466)	1.0 (18)	1.3 (246)	2.2 (158)	3.2 (453)	NA	1.9 (55)	2.2 (11)
Congestive cardiac failure	7.5 (3540)	6.6 (124)	5.0 (919)	8.8 (625)	6.7 (964)	5.9 (20)	5.6 (162)	7.1 (35)
Coronary heart disease	17.9 (8471)	18.9 (353)	13.5 (2488)	22.5 (1605)	17.9 (2560)	18.6 (63)	13.9 (401)	26.3 (129)
Diabetes	15.1 (7143)	17.0 (318)	15.1 (2780)	20.0 (1425)	14.0 (2007)	13.6 (46)	14.0 (404)	19.4 (95)
Dyspepsia	17.3 (8166)	16.9 (316)	17.3 (3193)	17.8 (1272)	24.5 (3502)	21.8 (74)	25.2 (730)	26.3 (129)
Falls or hip fracture*	7.2 (3405)	17.0 (317)	8.3 (1538)	6.6 (472)	5.8 (824)	6.5 (22)	5.8 (167)	6.5 (32)
Hip or knee operation*	3.1 (1445)	23.0 (430)	7.2 (1318)	3.7 (261)	5.2 (738)	30.7 (104)	8.2 (237)	6.7 (33)
Hypertension	40.5 (19 184)	51.3 (959)	40.0 (7363)	52.1 (3714)	43.3 (6200)	48.7 (165)	42.4 (1226)	54.9 (269)
Ischaemic stroke†	12.0 (5661)	20.6 (384)	10.5 (1937)	22.9 (1631)	11.6 (1663)	23.0 (78)	10.7 (309)	33.7 (165)
Oesophageal varices	0.3 (137)	NA	0.1 (18)	0.1 (6)	0.2 (29)	NA	NA	NA
Peptic ulcer	6.5 (3097)	7.0 (131)	5.6 (1040)	7.2 (513)	6.8 (979)	5.6 (19)	6.7 (195)	9.4 (46)
Valvular heart disease	8.7 (4133)	5.8 (108)	4.3 (791)	7.1 (506)	6.9 (982)	6.5 (22)	3.6 (103)	6.5 (32)
Venous thromboembolism†	58.0 (27 464)	8.5 (159)	39.2 (7222)	17.5 (1249)	62.9 (9003)	10.3 (35)	45.9 (1329)	21.2 (104)
Previous bleed:								
Any†	22.3 (10 552)	22.7 (424)	23.3 (4301)	23.8 (1697)	25.7 (3672)	25.4 (86)	26.4 (763)	31.6 (155)
Intracranial†	1.1 (534)	1.1 (21)	1.1 (207)	1.2 (87)	1.2 (177)	1.8 (6)	1.6 (46)	2.2 (11)
Haematuria	9.2 (4377)	9.7 (181)	9.6 (1775)	10.1 (721)	10.0 (1431)	10.3 (35)	9.0 (261)	11.8 (58)
Haemoptysis†	2.8 (1305)	2.4 (44)	2.6 (486)	2.5 (179)	3.3 (474)	3.5 (12)	4.0 (115)	4.7 (23)
Previous gastrointestinal bleed:†								
All	12.1 (5716)	12.5 (233)	13.0 (2400)	13.4 (955)	14.8 (2124)	13.6 (46)	15.5 (449)	16.9 (83)
Upper	4.2 (1995)	4.0 (74)	4.1 (754)	4.9 (350)	4.8 (687)	6.5 (22)	5.6 (163)	7.6 (37)
Lower	8.8 (4186)	9.5 (177)	10.1 (1856)	9.7 (694)	11.4 (1639)	8.6 (29)	11.8 (342)	11.8 (58)
Other drugs:								
Proton pump inhibitors	42.8 (20 259)	45.0 (841)	40.4 (7434)	42.7 (3042)	40.4 (5777)	44.8 (152)	40.8 (1181)	46.5 (228)
Antibiotics‡	11.0 (5222)	8.7 (162)	8.6 (1576)	5.6 (397)	10.1 (1452)	8.3 (28)	9.6 (277)	7.1 (35)
Antiplatelet	20.7 (9797)	21.6 (403)	16.4 (3014)	17.8 (1273)	22.5 (3216)	27.7 (94)	17.6 (508)	28.8 (141)
Antidepressants	21.9 (10 352)	19.8 (370)	22.2 (4094)	19.8 (1411)	20.9 (2992)	19.8 (67)	23.0 (664)	22.9 (112)
Anticonvulsants	1.5 (696)	0.8 (15)	1.2 (217)	1.0 (72)	1.4 (195)	1.5 (5)	1.3 (39)	NA
NSAIDs	12.1 (5722)	17.2 (321)	13.2 (2434)	5.7 (406)	12.0 (1723)	23.6 (80)	12.5 (361)	7.8 (38)
Corticosteroids	13.5 (6407)	9.2 (172)	10.5 (1934)	9.4 (670)	12.7 (1822)	10.3 (35)	11.4 (330)	11.2 (55)
Statins	39.6 (18 726)	49.1 (917)	35.3 (6507)	51.2 (3655)	37.3 (5333)	49.9 (169)	33.9 (980)	52.7 (258)
Hormones (women)	2.5 (546)	2.3 (20)	2.7 (257)	1.7 (58)	6.7 (449)	5.7 (9)	8.5 (130)	3.3 (8)

For information on age distribution, ethnicity, smoking, alcohol consumption, and Townsend quintiles see supplementary table 4.
NA=not applicable, fewer than 5 observations; NSAIDs=non-steroidal anti-inflammatory drugs.
*Within the last 6 months.
†Based on general practice and Hospital Episode Statistics records.
‡Within the last 6 months before the drug start date.

intracranial bleed than warfarin, and rivaroxaban was associated with a higher risk compared to apixaban (1.94, 1.19 to 3.16). Although no drugs were significantly different from warfarin in risks of any other bleeding events, rivaroxaban was associated with higher risks compared with apixaban for haematuria, all gastrointestinal bleed and upper gastrointestinal bleed (fig 3 and fig 5).

In the subcohort without atrial fibrillation, apixaban was associated with lower risks of major bleed (adjusted hazard ratio 0.60, 95% confidence interval 0.46 to 0.79) than warfarin (fig 4) or rivaroxaban

Table 3 | Patients with atrial fibrillation: age-sex standardised incidence rates per 1000 person years (py) of outcomes by database

	QResearch			CPRD		
Drug	Person years	No of events	Age-sex standardised rate per 1000 py (95% CI)	Person years	No of events	Age-sex standardised rate per 1000 py (95% CI)
Major bleeding						
Warfarin	72 487	1813	25.1 (24.0 to 26.3)	18 795	515	27.5 (25.1 to 29.8)
Dabigatran	4988	107	21.8 (17.7 to 26.0)	886	17	19.1 (10.0 to 28.3)
Rivaroxaban	12 515	338	26.5 (23.7 to 29.4)	1844	66	36.3 (27.4 to 45.1)
Apixaban	7471	119	15.4 (12.6 to 18.3)	768	22	29.0 (16.6 to 41.5)
Intracranial bleed						
Warfarin	73 776	448	6.2 (5.6 to 6.7)	19 080	112	5.9 (4.8 to 7.0)
Dabigatran	5082	14	3.0 (1.4 to 4.6)	894	<5	1.0 (0.0 to 3.0)
Rivaroxaban	12 668	66	5.1 (3.9 to 6.3)	1865	15	8.2 (4.0 to 12.5)
Apixaban	7508	22	2.6 (1.4 to 3.7)	774	<5	5.0 (0.0 to 10.0)
Haematuria						
Warfarin	73 105	585	8.0 (7.3 to 8.6)	18 948	158	8.3 (7.0 to 9.6)
Dabigatran	5040	33	6.4 (4.2 to 8.6)	890	7	7.3 (1.8 to 12.8)
Rivaroxaban	12 610	100	7.9 (6.4 to 9.5)	1853	21	11.6 (6.6 to 16.6)
Apixaban	7498	33	4.4 (2.9 to 5.9)	771	7	8.7 (2.1 to 15.2)
Haemoptysis						
Warfarin	73 755	107	1.4 (1.2 to 1.7)	19 069	27	1.4 (0.9 to 1.9)
Dabigatran	5067	8	1.4 (0.4 to 2.5)	894	<5	1.3 (0.0 to 3.8)
Rivaroxaban	12 669	18	1.4 (0.8 to 2.1)	1866	<5	1.2 (0.0 to 2.8)
Apixaban	7511	<5	0.5 (0.0 to 1.1)	774	<5	1.2 (0.0 to 3.6)
All gastrointestinal bleed						
Warfarin	73 360	691	9.5 (8.8 to 10.2)	18 978	224	11.8 (10.3 to 13.4)
Dabigatran	5047	54	11.2 (8.2 to 14.2)	890	8	9.4 (2.9 to 15.9)
Rivaroxaban	12 603	158	12.1 (10.2 to 14.1)	1858	30	16.0 (10.2 to 21.9)
Apixaban	7489	62	8.2 (6.1 to 10.2)	771	10	14.1 (5.2 to 23.0)
Upper gastrointestinal bleed						
Warfarin	73 424	617	8.5 (7.8 to 9.1)	18 989	204	10.7 (9.3 to 12.2)
Dabigatran	5047	53	11.0 (8.0 to 14.0)	891	7	8.0 (2.1 to 14.0)
Rivaroxaban	12 612	149	11.5 (9.6 to 13.3)	1858	29	15.5 (9.8 to 21.2)
Apixaban	7491	58	7.6 (5.6 to 9.7)	772	9	12.6 (4.2 to 20.9)
Rectal bleed						
Warfarin	73 769	78	1.1 (0.8 to 1.3)	19 081	22	1.2 (0.7 to 1.7)
Dabigatran	5082	<5	0.3 (0.0 to 0.8)	893	<5	1.4 (0.0 to 4.0)
Rivaroxaban	12 670	9	0.7 (0.2 to 1.1)	1866	<5	0.6 (0.0 to 1.6)
Apixaban	7509	5	0.6 (0.1 to 1.2)	773	<5	1.5 (0.0 to 4.5)
Ischaemic stroke						
Warfarin	59 343	794	13.5 (12.6 to 14.5)	15 349	225	14.7 (12.8 to 16.6)
Dabigatran	3744	58	15.9 (11.8 to 20.1)	642	7	11.4 (2.7 to 20.2)
Rivaroxaban	10 278	128	12.0 (9.9 to 14.1)	1434	34	23.6 (15.5 to 31.7)
Apixaban	5573	86	15.2 (11.9 to 18.5)	535	9	16.4 (5.5 to 27.3)
Venous thromboembolism						
Warfarin	69 569	215	3.1 (2.7 to 3.5)	17 676	68	3.8 (2.9 to 4.8)
Dabigatran	4921	6	1.2 (0.2 to 2.2)	846	<5	1.3 (0.0 to 3.9)
Rivaroxaban	11 992	50	4.1 (2.9 to 5.2)	1726	12	6.7 (2.8 to 10.6)
Apixaban	7230	19	2.5 (1.3 to 3.6)	726	5	6.8 (0.6 to 13.0)
Mortality						
Warfarin	73 839	3183	44.6 (43.0 to 46.1)	19 094	780	41.7 (38.7 to 44.6)
Dabigatran	5083	212	43.1 (37.3 to 49.0)	894	38	41.9 (28.4 to 55.5)
Rivaroxaban	12 679	757	54.6 (50.6 to 58.6)	1866	112	53.2 (42.9 to 63.4)
Apixaban	7511	472	53.5 (48.4 to 58.5)	774	56	61.9 (45.0 to 78.9)

(fig 5). Rivaroxaban was associated with a lower risk of intracranial bleed (0.54, 0.35 to 0.82) compared with warfarin, and apixaban with lower risks of all gastrointestinal (0.55, 0.37 to 0.83) and upper gastrointestinal bleeds (0.55, 0.36 to 0.83). Dabigatran and rivaroxaban were associated with higher risks for all gastrointestinal bleeds compared with apixaban, rivaroxaban was also associated with a higher risk for upper gastrointestinal bleed (fig 5).

The risk of primary ischaemic stroke did not differ between any of the anticoagulants studied in either subcohort. Figure 4 shows that the risk of primary venous thromboembolism in patients with atrial fibrillation was not different between any drugs, but

Table 4 | Patients without atrial fibrillation: age-sex standardised incidence rates per 1000 person years (py) of outcomes by database

	QResearch			CPRD		
Drug	Person years	No of events	Age-sex standardised rate per 1000 py (95% CI)	Person years	No of events	Age-sex standardised rate per 1000 py (95% CI)
Major bleeding						
Warfarin	39 335	1132	29.2 (27.5 to 30.9)	10 796	378	35.2 (31.6 to 38.7)
Dabigatran	1129	33	31.0 (18.8 to 43.1)	183	6	28.6 (4.2 to 53.0)
Rivaroxaban	8066	238	29.4 (25.6 to 33.1)	1143	41	34.9 (24.0 to 45.7)
Apixaban	3273	71	18.3 (13.6 to 23.1)	219	<5	5.9 (0.0 to 13.0)
Intracranial bleed						
Warfarin	39 929	244	6.3 (5.5 to 7.1)	10 952	78	7.2 (5.6 to 8.8)
Dabigatran	1137	<5	2.9 (0.0 to 5.8)	184	<5	3.5 (0.0 to 10.3)
Rivaroxaban	8155	29	3.5 (2.2 to 4.8)	1156	<5	2.7 (0.0 to 5.4)
Apixaban	3297	19	5.2 (2.7 to 7.7)	220	0	NA
Haematuria						
Warfarin	39 685	351	8.9 (8.0 to 9.8)	10 897	109	10.0 (8.1 to 11.9)
Dabigatran	1133	8	7.9 (2.0 to 13.8)	184	<5	8.4 (0.0 to 25.0)
Rivaroxaban	8119	71	9.0 (6.9 to 11.1)	1150	11	9.2 (3.7 to 14.7)
Apixaban	3291	21	4.3 (2.4 to 6.1)	219	<5	3.0 (0.0 to 7.2)
Haemoptysis						
Warfarin	39 912	65	1.6 (1.2 to 2.0)	10 950	24	2.2 (1.3 to 3.0)
Dabigatran	1137	<5	2.3 (0.0 to 5.5)	184	0	NA
Rivaroxaban	8151	16	1.9 (1.0 to 2.9)	1155	<5	3.8 (0.1 to 7.6)
Apixaban	3300	<5	0.3 (0.0 to 0.8)	220	0	NA
All gastrointestinal bleed						
Warfarin	39 684	485	12.4 (11.3 to 13.5)	10 885	171	15.9 (13.5 to 18.2)
Dabigatran	1133	19	17.7 (8.1 to 27.4)	184	<5	16.6 (0.1 to 33.1)
Rivaroxaban	8114	126	15.2 (12.5 to 17.9)	1150	22	18.8 (10.8 to 26.9)
Apixaban	3286	31	8.8 (5.2 to 12.3)	220	<5	2.9 (0.0 to 8.6)
Upper gastrointestinal bleed						
Warfarin	39 719	431	11.1 (10.0 to 12.1)	10 896	152	14.1 (11.9 to 16.4)
Dabigatran	1134	16	15.6 (6.3 to 24.9)	184	<5	16.6 (0.1 to 33.1)
Rivaroxaban	8116	117	14.0 (11.5 to 16.6)	1150	22	18.8 (10.8 to 26.8)
Apixaban	3288	29	8.0 (4.6 to 11.4)	220	<5	2.9 (0.0 to 8.6)
Rectal bleed						
Warfarin	39 917	62	1.6 (1.2 to 2.0)	10 949	21	1.9 (1.1 to 2.7)
Dabigatran	1136	<5	2.1 (0.0 to 4.6)	184	0	NA
Rivaroxaban	8155	9	1.1 (0.4 to 1.9)	1156	0	NA
Apixaban	3298	<5	0.7 (0.0 to 1.8)	220	0	NA
Ischaemic stroke						
Warfarin	34 121	371	11.2 (10.1 to 12.4)	9459	109	11.6 (9.4 to 13.8)
Dabigatran	755	19	20.8 (10.7 to 30.9)	117	<5	21.1 (0.0 to 45.1)
Rivaroxaban	6996	83	11.8 (9.2 to 14.3)	990	9	7.9 (2.6 to 13.3)
Apixaban	2311	44	15.4 (10.6 to 20.3)	121	<5	17.5 (0.0 to 37.3)
Venous thromboembolism						
Warfarin	18 496	766	41.0 (38.1 to 44.0)	4526	182	40.0 (34.2 to 45.9)
Dabigatran	1055	10	9.7 (3.5 to 15.9)	166	6	35.1 (5.0 to 65.1)
Rivaroxaban	4001	688	180.3 (166.5 to 194.1)	532	112	239.7 (193.7 to 285.8)
Apixaban	2748	89	44.0 (33.4 to 54.7)	188	<5	11.7 (0.0 to 25.0)
Mortality						
Warfarin	39 960	2226	58.4 (56.0 to 60.8)	10 963	606	56.6 (52.1 to 61.1)
Dabigatran	1137	75	67.4 (41.7 to 93.0)	184	14	60.1 (26.9 to 93.2)
Rivaroxaban	8158	758	87.1 (80.8 to 93.3)	1156	130	108.4 (89.3 to 127.6)
Apixaban	3301	312	72.8 (63.9 to 81.7)	220	21	86.2 (25.4 to 146.9)

NA=not applicable.

in the subcohort without atrial fibrillation compared with warfarin there was a higher risk in patients taking rivaroxaban (adjusted hazard ratio 1.49, 95% confidence interval 1.33 to 1.68) and lower risks in patients taking dabigatran (0.25, 0.15 to 0.41) and apixaban (0.42, 0.33 to 0.53).

For both patients with atrial fibrillation (adjusted hazard ratio 1.19, 95% confidence interval 1.09 to 1.29) and without atrial fibrillation (1.51, 1.38 to 1.66), the risk of mortality was increased in patients taking rivaroxaban compared with warfarin. Although the estimates for apixaban in both subcohorts were

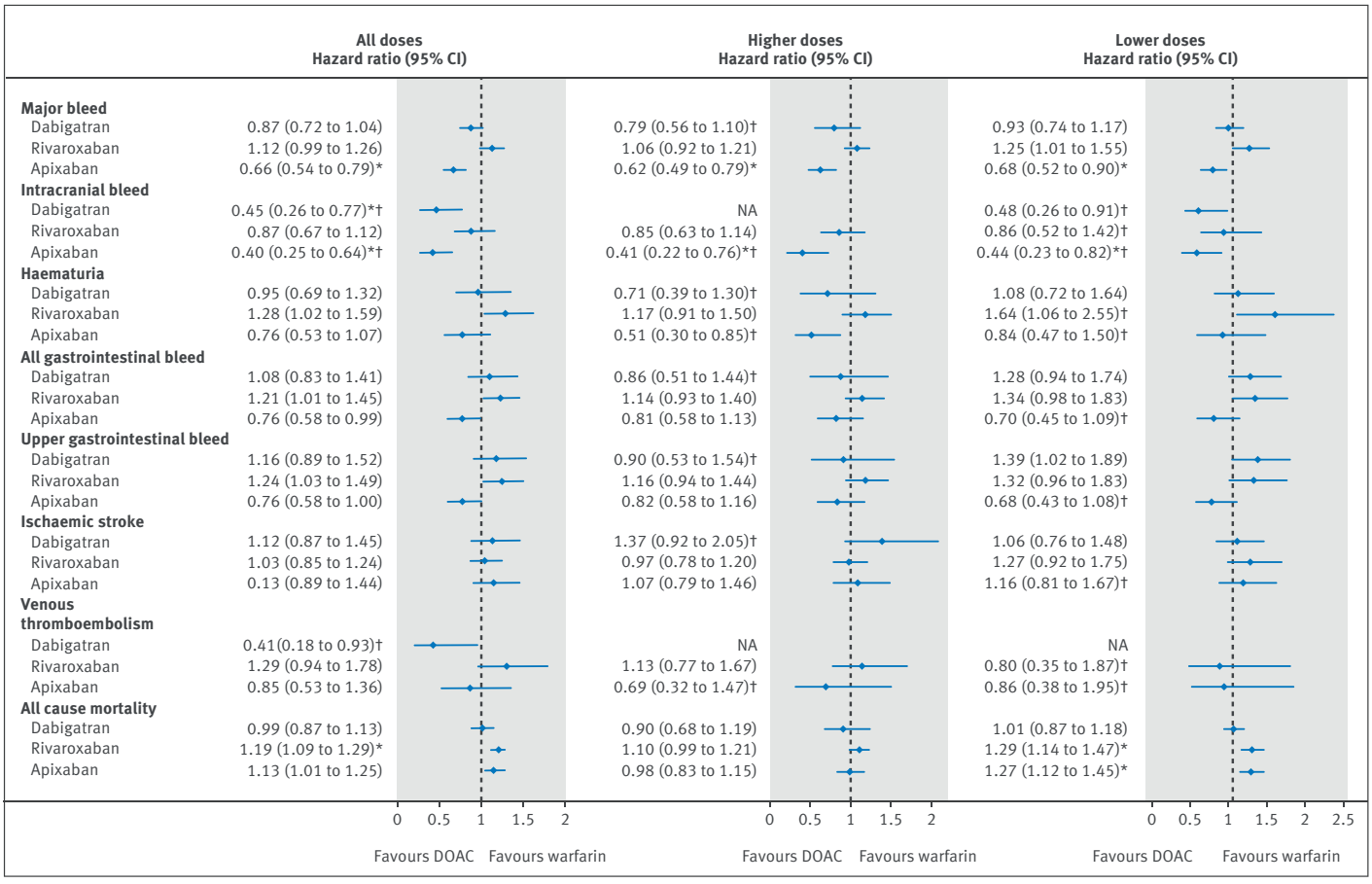

Fig 3 | Patients with atrial fibrillation: adjusted Cox hazard ratios (95% confidence interval) for outcomes associated with exposure to study drugs overall and by prescribed dose compared with warfarin. NA=not available. *P value<0.01. †The results were only available from the QResearch database.

higher than unity (1.13, 1.01 to 1.26 for patients with atrial fibrillation; 1.16, 1.02 to 1.33 for patients without atrial fibrillation) and neither of them were statistically significant (at P<0.01), the estimate for the whole cohort was (adjusted hazard ratio 1.14, 95% confidence interval 1.05 to 1.24, P=0.001) (see supplementary figure 1 and supplementary table 5). Supplementary table 8 shows that most of these deaths were owing to causes other than bleeding, ischaemic stroke, or venous thromboembolism (91% in QResearch and 88% in CPRD).

Numbers needed to harm and treat

Table 5 shows the number needed to treat or number needed to harm to measure the relative benefits or risks of DOACs in comparison with warfarin. In the subcohort with atrial fibrillation, over six months, the lowest number needed to treat (to avoid one extra major bleed) was for apixaban (182, 95% confidence interval 137 to 299). The lowest number needed to harm (to observe one extra death) over six months was for rivaroxaban (202, 131 to 410). In the subcohort without atrial fibrillation, over six months, the lowest number needed to treat to avoid one extra major bleed was also for apixaban (138, 102 to 207). The lowest number needed to harm for deaths was again for rivaroxaban (61, 47 to 82).

Dose analysis

Overall, patients on lower doses of DOACs were older, had more comorbidities, previous events, and other drugs than patients on higher doses (see supplementary tables 9 and 10). In the subcohort with atrial fibrillation, patients on lower doses were on average 10 years older (mean 83 years *v* 73 across the databases), more likely to be women (58% *v* 41%), more likely to be non-drinkers (42% *v* 30%), more likely to have lower body mass index (mean 27 kg/m^2 *v* 29 kg/m^2), and more likely to have age associated morbidities, including hypertension (67% *v* 57%), congestive cardiac failure (17% *v* 10%), coronary heart disease (29% *v* 20%), valvular heart disease (12% *v* 8%), and chronic renal disease (4% *v* 1%). Patients on lower doses were also more likely to have had falls or hip fracture (12% *v* 6%) (see supplementary tables 9 and 10).

In the subcohort without atrial fibrillation, patients on lower doses of DOACs were on average 7 years older (mean 75 years *v* 68 across the databases), more likely to be women (59% *v* 48%), more likely to be non-drinkers (40% *v* 34%), and more likely to have age associated comorbidities, with diagnoses of hypertension (52% *v* 41%), congestive cardiac failure (9% *v* 5%), coronary heart disease (20% *v* 15%), valvular heart disease (7% *v* 4%), and chronic renal disease (3% *v* 1%) than patients on higher doses. Patients on lower doses were also

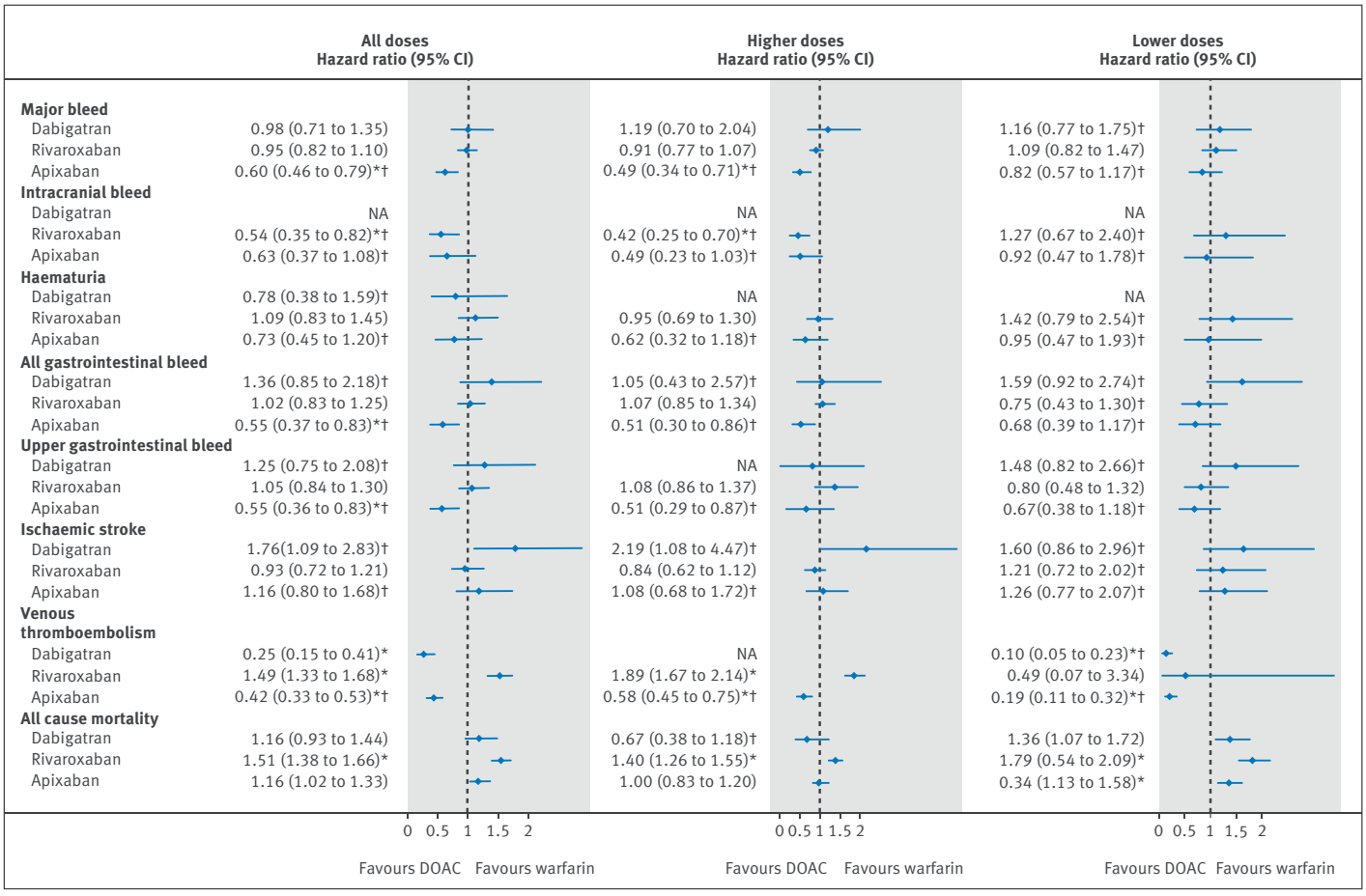

Fig 4 | Patients without atrial fibrillation: adjusted Cox hazard ratios (95% confidence interval) for outcomes associated with exposure to study drugs overall and by prescribed dose compared with warfarin. NA=not available. *P value<0.01. †The results were only available from the QResearch database.

more likely to have had falls or hip fracture (16% *v* 5%), hip or knee replacement operations (22% *v* 3%), and previous ischaemic stroke (18% *v* 13%). The proportion of patients with previous venous thromboembolism was lower than in the higher dose group (15% *v* 38%) (see supplementary tables 9 and 10).

Age-sex standardised rates for patients on lower and higher doses and adjusted hazard ratios with reference to warfarin are shown for the subcohort with atrial fibrillation in supplementary table 11 and for the subcohort without atrial fibrillation in supplementary table 12. Although higher doses were mainly associated with lower risks than lower doses, the confidence intervals for the adjusted hazard ratios overlapped for most outcomes and drugs (see fig 3 for patients with atrial fibrillation, fig 4 for patients without atrial fibrillation, and supplementary table 13 with supplementary figure 1 for all patients). In patients with atrial fibrillation, only low doses of rivaroxaban (adjusted hazard ratios of 1.29, 95% confidence interval 1.14 to 1.47) and apixaban (1.27, 1.12 to 1.45) were associated with an increased risk of mortality. In patients without atrial fibrillation, however, both low and high doses of rivaroxaban were associated with increased risks while for apixaban only low doses were associated with increased risk of mortality (1.34, 1.13 to 1.58).

Sensitivity analyses

Analyses for ethnicity, where unrecorded values were included as a separate category, also obtained very similar results. Reanalysis of the whole cohort, but with patients censored if admitted to hospital for bleeding, ischaemic stroke, or venous thromboembolism, gave results which were very similar to the main analysis for all outcomes (see supplementary table 14). Results from the complete case analysis were comparable to the main analysis (see supplementary table 15). Analyses adjusted with propensity scores also resulted in similar hazard ratios compared with the complete case analysis (see supplementary table 15).

Discussion

Our study, based on routinely collected care data, showed a decreased risk of major bleeding events associated with the use of apixaban compared with warfarin in both patients with atrial fibrillation and without atrial fibrillation. Similarly, in patients with atrial fibrillation, a lower risk of intracranial bleed was associated with dabigatran and apixaban. In patients without atrial fibrillation, use of rivaroxaban was associated with a lower risk of intracranial bleed and apixaban was associated with lower risks of any gastrointestinal bleed and upper gastrointestinal

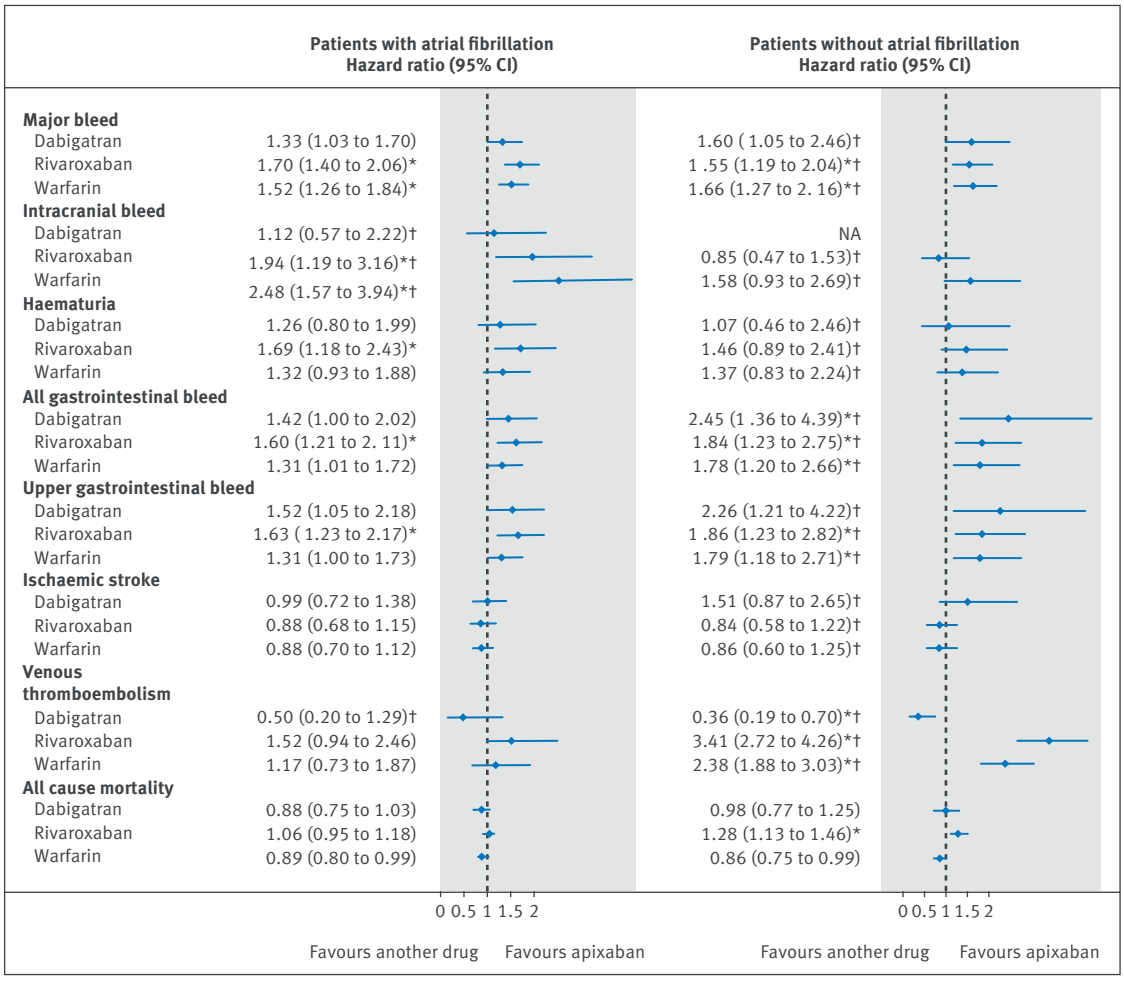

Fig 5 | Patients with and without atrial fibrillation: adjusted Cox hazard ratios (95% confidence interval) for outcomes associated with exposure to study drugs compared with apixaban. NA=not available. *P value<0.01. †The results were only available from the QResearch database.

bleeds. In both patients with atrial fibrillation and without atrial fibrillation, rivaroxaban and lower doses of apixaban were associated with an increased risk of all cause mortality compared with warfarin.

Strengths and weaknesses of this study

The study, using the two largest primary care databases in the UK to deliver high statistical power, contributes to the evidence from other major studies. The general practice records were linked to hospital and mortality data, so all recorded outcomes were identified. Consistency in records of comorbidities, lifestyle, and prescribing across the databases also facilitated the combination of results from each, so delivering narrower confidence intervals for our estimations.

An important limitation for our study and all earlier observational studies is the lack of information on patient adherence to their prescribed drugs, which may lead to possible misclassifications of exposure. It is not known when exactly a patient stopped taking anticoagulants, and our setting of 30 days as a period during which they could still have been exposed was selected primarily to make our study consistent with – and therefore comparable to – previous research. Warfarin has been shown to have the highest non-persistence and apixaban and rivaroxaban the lowest.[41] A study based on routinely collected data has shown that adding international normalisation ratio information, which we could not use directly because of inconsistent recording, could increase the estimate of exposure to vitamin K antagonists by 13% to 18% over 12 months.[42] In our sample, the median duration of exposure to warfarin was less than a year, so our addition of 30 days to exposure will to some extent have compensated for this lack of information regarding warfarin exposure. However, despite the addition of this 30 day grace period to each anticoagulant course, there is still uncertainty about precise periods of exposure.

The effect of non-adherence on bleeding rates has also been shown using commercial insurance data and non-adherence is likely to have contributed to various extents to underestimation of the efficacy of any of the drugs in our study with respect to the prevention of ischaemic stroke or venous thromboembolism.[43] With respect to mortality outcomes, a greater proportion of the older patients on apixaban and rivaroxaban may have died while still taking anticoagulants, but from age

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Table 5 | Number needed to treat or harm (95% confidence interval) compared with warfarin

Outcome	6 months	12 months	18 months	24 months
With atrial fibrillation				
Numbers needed to treat:				
Major bleeding, apixaban	182 (137 to 299)	104 (78 to 170)	76 (58 to 126)	60 (45 to 99)
Intracranial bleed, dabigatran	545 (407 to 1310)	274 (204 to 658)	196 (146 to 472)	150 (111 to 360)
Intracranial bleed, apixaban	501 (401 to 828)	252 (201 to 416)	180 (144 to 298)	137 (110 to 227)
Numbers needed to harm:				
Mortality, rivaroxaban	202 (131 to 410)	118 (76 to 239)	86 (56 to 175)	70 (45 to 141)
Without atrial fibrillation				
Numbers needed to treat:				
Major bleeding, apixaban	138 (102 to 257)	85 (62 to 158)	61 (45 to 114)	49 (36 to 91)
Intracranial bleed, rivaroxaban	592 (423 to 1528)	323 (230 to 834)	224 (160 to 579)	185 (132 to 479)
All gastrointestinal bleed, apixaban	293 (207 to 756)	181 (128 to 467)	126 (89 to 326)	96 (68 to 248)
Upper gastrointestinal bleed, apixaban	329 (232 to 891)	200 (141 to 543)	138 (97 to 375)	108 (76 to 294)
Venous thromboembolism,* dabigatran	34 (30 to 43)	32 (28 to 40)	30 (27 to 39)	29 (26 to 37)
Venous thromboembolism,* apixaban	44 (38 to 55)	41 (35 to 51)	40 (34 to 49)	38 (33 to 47)
Numbers needed to harm:				
Venous thromboembolism,* rivaroxaban	53 (38 to 80)	49 (36 to 75)	48 (34 to 72)	46 (33 to 69)
Mortality, rivaroxaban	61 (47 to 82)	37 (29 to 49)	27 (21 to 37)	23 (18 to 30)

The calculations are based on the hazard ratios derived from QResearch or combined analysis. Only statistically significant associations between the exposure and outcome are included.
*Based on patients without venous thromboembolism before the start of anticoagulant

related causes other than ischaemic stroke or venous thromboembolism. We decided to adjust for a diagnosis of chronic kidney disease in the analysis rather than undertake a detailed analysis of renal function through the analysis of individual blood tests. A reduced dose of direct oral anticoagulant (DOAC) is recommended in patients with renal impairment as well as for patients aged over 80 and under 60 kg and there were more patients diagnosed with chronic renal disease in all lower dose DOAC groups, particularly in the apixaban and rivaroxaban groups. We adjusted for renal disease and for age and body mass index, but renal disease and use of anticoagulants may still contribute to mortality rate and this needs further research.[44]

An increased risk of bleeding in patients taking warfarin compared to those taking a DOAC could be because of the regular monitoring required for warfarin users. Bleeds could be more likely to be detected in these patients than in those taking DOACs, introducing a surveillance bias. Our definition of the outcome as any bleed requiring admission to hospital or causing death makes it less likely that these would be missed in the patients taking DOACs. However, a minor bleed detected in warfarin users could have been treated before it developed into a more serious one.

Included patients had different indications for anticoagulation and the DOAC groups were generally older and less healthy than the comparator warfarin group. Extensive adjustment for confounders, however, should have helped to reduce possible indication bias.

Exposure in our study was based only on GP records, without information from other possible sources of anticoagulants such as anticoagulant clinics or hospital stays. A small proportion of patients might have had private health insurance with prescriptions not available on the GP records. In the UK, however, the overwhelming proportion of events included as outcomes in this study would not be treated using private medical care. There is also some uncertainty surrounding venous thromboembolism diagnoses in QResearch and Clinical Practice Research Datalink (CPRD) cohorts because the results of diagnostic tests are not available to researchers in primary care records. This might lead to a misclassification of the outcome and a slightly increased rate of venous thromboembolism. It may, however, happen to patients taking any anticoagulant and we are not aware of any systematic differences between the prescribing of these drugs, but we accept a possible shift in results towards unity. The findings regarding risk of venous thromboembolism associated with different anticoagulants should, however, be interpreted with caution.

These uncertainties could have affected our results in several ways. We may have included some patients who had had exposure to anticoagulants in the 12 months before their entry. Included patients admitted to hospital for bleeding events might also have stopped anticoagulant therapy and then suffered an ischaemic stroke, developed venous thromboembolism, or died, so causing their misclassification as anticoagulant users. Our sensitivity analysis censoring such patients did not, however, require alterations to our conclusions. We also lacked information about over-the-counter purchases of other drugs such as a non-steroidal anti-inflammatory drug or aspirin, but this is likely to have affected only a small number of patients.

Between QResearch and CPRD most of the results were consistent, but there were a few differences in rates and hazard ratios. This is not unexpected, partly owing to small numbers for some comparisons and because contributing practices for the two databases not only use different computer systems for data collection but also have somewhat different profiles in terms of their location within different geographical regions.[45]

This is an observational study with high quality information on which drugs have been prescribed, the dates and duration. However, limitations include lack of information on adherence and all the indications for prescribing. Although many adjustments have been done using the data available on the existing databases, there is a possibility of unmeasured confounding or confounding by indication. Routinely collected data are also not always consistently recorded and information stored in free text format is not extracted from the GP systems. Only available, consistently recorded variables can be used in such studies, which always creates the possibility of some residual confounding.

Strengths and weaknesses in relation to other studies

Incidence rates of outcomes in general for patients taking anticoagulants depend on a number of study design factors. One is inclusion criteria, with incidence rates being lower for cohorts excluding patients with previous events. Another, the duration of the grace period after a prescription ends but when the patient is still considered exposed, may result in incidence rates being lower in studies with a shorter grace period. Grace periods were not consistent across the studies, ranging from three to 30 days, with studies in Denmark assuming continuous treatment.[18 22] Our rates were much higher than the rates from the Danish studies and from studies using US insurance data.[12 15 16 20]

This was a large comprehensive study using the most recent data, so one of the study strengths is its representativeness in terms of new users (or restarters) of anticoagulant drugs. All data were routinely collected and included not only comorbidities and any drugs but information on lifestyle factors such as smoking and alcohol – not commonly used in previous studies.[12 15 17 18 21 22]

Atrial fibrillation is one of the most common indications for anticoagulant prescribing, so almost all observational studies provide evidence for this restricted group. Approximately the same numbers of patients without atrial fibrillation are, however, also prescribed anticoagulants, creating a gap in knowledge about the effects of these drugs. Such patients are different in their comorbidities and indications for prescribing, so the risks of ischaemic stroke, venous thromboembolism, and mortality are unlikely to be the same.

It is difficult to discern the precise indications for anticoagulation. Not every patient diagnosed with atrial fibrillation is prescribed anticoagulants.[46] Some patients in the atrial fibrillation subcohort also had hip fractures or operations which could have required anticoagulation. We believe that our findings for all anticoagulant users, although presented separately for patients with and without atrial fibrillation, provide more generalisable evidence than findings based only on the subset of patients with atrial fibrillation. For patients without atrial fibrillation, however, presenting aggregated results can only highlight overall risks associated with DOAC drugs without being able to be more specific about underlying associations between different drugs and different conditions.

To facilitate comparison with other studies, our study offers analyses separately for patients with atrial fibrillation and without atrial fibrillation, and for patients on different DOAC doses. Although we used a proportional hazard model adjusting for all available confounding factors, we also undertook a sensitivity analysis using the propensity score method and obtained very similar results.

Important similarities and differences in results

Although patients with valvular heart disease were excluded from some trials and observational studies for patients with atrial fibrillation, a meta-analysis has shown that DOAC risks compared with warfarin for bleeding, ischaemic stroke, or systemic embolism and for death were similar for patients with atrial fibrillation with or without valvular heart disease.[47] For the main outcome of major bleeding, results from our study for the subcohort with atrial fibrillation were consistent with existing evidence from randomised controlled trials.[11] Apixaban appeared to be associated with the lowest risk of major bleeding in most of the larger studies.[12 14 18 20 21] The risk of mortality in our subcohort with atrial fibrillation was similar for warfarin, dabigatran, and apixaban but elevated for rivaroxaban. Like the Danish study,[22] our risk of mortality in this subcohort was elevated only for patients on lower doses of apixaban and rivaroxaban. The other Danish study of standard dosage showed decreased mortality for apixaban,[18] but our findings showed equivalent risk to warfarin for such patients.

The risk of ischaemic stroke associated with DOACs in our subcohort of patients with atrial fibrillation was equivalent to warfarin, which is in line with the latest meta-analysis for prevention of ischaemic stroke and both Danish studies.[11 18 22] Similarly, we did not show any different risks of venous thromboembolism for any DOACs compared with warfarin in patients with atrial fibrillation, which is also in line with the relevant findings from the latest meta-analysis.[11]

Meaning of the study: possible explanations and implications for clinicians and policy makers

Anticoagulants are prescribed for a wide range of indications although the adverse events have been studied mostly in patients with atrial fibrillation.[12-24] Our study has shown that the risk of major bleeding is lower in patients taking apixaban regardless of the reason for prescribing. This was most pronounced for intracranial bleeding in patients with atrial fibrillation and for gastrointestinal bleeding in patients without atrial fibrillation, appearing, in general, to show apixaban to be the safest drug.

Increased risk of all cause mortality was found in rivaroxaban users for both patients with atrial fibrillation and without atrial fibrillation. Apixaban was associated with an increased risk of all cause mortality in patients with atrial fibrillation and without atrial fibrillation, but only in patients on

lower doses. The increased all cause mortality may be reflecting the closer monitoring of patients undergoing treatment with warfarin may be related to unmeasured confounding due to prescribing choices related to underlying comorbidities.

Unanswered questions and future research

The use of DOACs in patients with atrial fibrillation has been extensively studied but this group represents only half of anticoagulant users. Our study provides the evidence for this group and highlights increased all cause mortality in the group of patients without atrial fibrillation indications for anticoagulant prescribing. This group, however, includes patients undergoing preventative treatment for venous thromboembolism or ischaemic stroke after hip or knee replacements, fractures, or other operations and studying this group in detail would require further splitting.

We were unable to investigate the risks of ischaemic stroke and venous thromboembolism in patients who had already experienced a prior event because it can be difficult to distinguish new events from ongoing reviews of previous events in electronic health records. The risk of bleeding was lower in patients taking DOACs but the risk of mortality was increased in rivaroxaban and lower dose apixaban users. This also requires further investigation.

Conclusion

This large observational study, based on a general population in a primary care setting, provides reassurance about the safety of DOACs as an alternative to warfarin across all new incident users. Apixaban was found to be associated with a decreased risk of major bleeding, particularly for intracranial and gastrointestinal bleeds. This was consistent for patients with atrial fibrillation and without atrial fibrillation. Rivaroxaban and low dose apixaban were, however, associated with an increased risk of all cause mortality when compared with warfarin. Our results give an initial, reassuring, indication of the risk patterns for all patients taking anticoagulants, with respect to those prescribed apixaban.

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Contributors: JHC initiated the study, undertook the original literature review, prepared the grant application, designed the study, drafted the study protocol, organised the extraction of the QResearch data, advised on clinical aspects of the study, interpreted the results, and critically reviewed the paper. CC contributed to the development of the idea, the study design, and advised on the analysis and interpretation of the results. TH did preliminary analyses of the data. YV reviewed the literature, contributed to the grant application and the study design, organised the extraction of Clinical Practice Research Datalink (CPRD) data, did the analysis on both datasets, and wrote the draft of the manuscript. JHC, CC, and TH critically reviewed the paper. YV is the guarantor of the study. All authors have approved the submitted version.

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Ethical approval: The protocol for QResearch has been published in eprints and was reviewed in accordance with the requirements for the East Midlands Derby Research Ethic Committee (ref 03/4/021).[48] The protocol for CPRD has been approved by The Independent Scientific Advisory Committee for MHRA Database Research (N 16_284R).

Data sharing: To guarantee the confidentiality of anonymised patient data and health information only the authors have had access to the data during the study in accordance with the relevant licence agreements. Access to the QResearch data are according to the information on the QResearch website (www.qresearch.org). Clinical Practice Research Datalink (CPRD) linked data were provided under a licence that does not permit sharing.

Transparency: The lead author (YV) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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Supplementary information: Supplementary tables 1-15
Supplementary information: Supplementary figure 1

ORIGINAL ARTICLE

Sudden Cardiac Arrest during Participation in Competitive Sports

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ABSTRACT

BACKGROUND

The incidence of sudden cardiac arrest during participation in sports activities remains unknown. Preparticipation screening programs aimed at preventing sudden cardiac arrest during sports activities are thought to be able to identify at-risk athletes; however, the efficacy of these programs remains controversial. We sought to identify all sudden cardiac arrests that occurred during participation in sports activities within a specific region of Canada and to determine their causes.

METHODS

In this retrospective study, we used the Rescu Epistry cardiac arrest database (which contains records of every cardiac arrest attended by paramedics in the network region) to identify all out-of-hospital cardiac arrests that occurred from 2009 through 2014 in persons 12 to 45 years of age during participation in a sport. Cases were adjudicated as sudden cardiac arrest (i.e., having a cardiac cause) or as an event resulting from a noncardiac cause, on the basis of records from multiple sources, including ambulance call reports, autopsy reports, in-hospital data, and records of direct interviews with patients or family members.

RESULTS

Over the course of 18.5 million person-years of observation, 74 sudden cardiac arrests occurred during participation in a sport; of these, 16 occurred during competitive sports and 58 occurred during noncompetitive sports. The incidence of sudden cardiac arrest during competitive sports was 0.76 cases per 100,000 athlete-years, with 43.8% of the athletes surviving until they were discharged from the hospital. Among the competitive athletes, two deaths were attributed to hypertrophic cardiomyopathy and none to arrhythmogenic right ventricular cardiomyopathy. Three cases of sudden cardiac arrest that occurred during participation in competitive sports were determined to have been potentially identifiable if the athletes had undergone preparticipation screening.

CONCLUSIONS

In our study involving persons who had out-of-hospital cardiac arrest, the incidence of sudden cardiac arrest during participation in competitive sports was 0.76 cases per 100,000 athlete-years. The occurrence of sudden cardiac arrest due to structural heart disease was uncommon during participation in competitive sports. (Funded by the National Heart, Lung, and Blood Institute and others.)

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The occurrence of sudden cardiac arrest in young persons during participation in competitive sports is a rare but tragic event. In numerous jurisdictions, preparticipation screening systems have been implemented on the assumption that most cases of sudden cardiac arrest that occur during sports activities can be predicted and prevented by identifying persons at risk, withdrawing them from competitive sports, and in selected cases, applying therapeutic preventive measures.[1,2]

The reported incidence of sudden cardiac death in the young (usually defined as <35 years of age) — with sudden cardiac death referring exclusively to sudden cardiac arrest that results in death — ranges widely, from 1.0 to 6.4 cases per 100,000 patient-years.[3] The instantaneous risk of sudden cardiac arrest in persons who have a predisposition to sudden cardiac arrest is markedly increased during participation in sports, even though most sudden cardiac arrests occur while the person is at rest.[4] The incidence of sudden cardiac death during participation in a sport in the general population has been reported to be approximately 0.46 cases per 100,000 person-years.[5]

The uncertainty regarding the precise incidence of sudden cardiac arrest in the young, particularly during participation in a sport, can be attributed in part to imperfect data collection systems that have been used in previous studies. Almost all the studies have focused on persons who could not be resuscitated (sudden cardiac deaths), and in most of the studies, death certificates, hospital records, autopsy reports, or searches of publicly available records were used to identify cases of sudden cardiac arrest.[3-10] These approaches are limited because systematic methods were not used to identify all persons in a particular community who had sudden cardiac arrest and because survivors were not included.

Rescu Epistry is a prospective, comprehensive registry of all persons who had out-of-hospital cardiac arrest and whose event was attended by emergency medical services (EMS) personnel in a defined region of the province of Ontario, Canada. This validated registry allows an opportunity to systematically examine the circumstances and causes of out-of-hospital cardiac arrest to quantify how many of the events are truly sudden and how many are truly cardiac in origin.[11] We used this registry to ascertain the incidence of sudden cardiac arrest during participation in competitive and noncompetitive sports activities among young persons and to determine the underlying causes. Currently, no widespread systematic programs to screen persons before participation in a sport are in place in Canada[12]; the current analysis allowed us to estimate the potential efficacy of systematic preparticipation screening.

METHODS

STUDY DESIGN

In this retrospective study, we identified out-of-hospital cardiac arrests using the population-based Rescu Epistry cardiac arrest database, which is based on data definitions from the Cardiac Arrest Registry of the Resuscitation Outcomes Consortium[13] database and the Strategies for Post Arrest Resuscitation Care Network[11] database. In brief, the Rescu Epistry database is a prospective, population-based registry of consecutive out-of-hospital cardiac arrests attended by EMS personnel who were responding to 911 calls in a specific area of Ontario, including both urban and rural regions, that has a combined population of 6.6 million (see Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Data are collected from a network of seven land-based EMS agencies, local fire departments, the provincial air ambulance service, and 44 participating destination hospitals. Trained personnel enter epidemiologic data from standardized prehospital call reports and in-hospital records into secured databases. Potential out-of-hospital cardiac arrests that are missed by Rescu Epistry are assumed to be expected deaths for which an advance directive is in place or for which the treating physician arranges for body removal services without involving EMS. Such deaths must meet legislated criteria that define obvious death.

The St. Michael's Hospital research ethics board provided ethics approval for the study. The study was supported by the National Heart, Lung, and Blood Institute, the Canadian Institutes of Health Research, and others. None of the organizations that funded the study had any role in the design or conduct of the study; in the collection, management, analysis, or interpretation

of the data; or in the preparation, review, or approval of the manuscript for submission. All the authors vouch for the completeness and accuracy of the data and the analyses.

KEY DEFINITIONS

We defined out-of-hospital cardiac arrest as an event that did not occur in a hospital, was attended by EMS personnel, may or may not have been witnessed, was associated with an abrupt loss of vital signs, and resulted either in death or in successful resuscitation.[14] We defined sudden cardiac arrest as an unexpected out-of-hospital cardiac arrest that occurred abruptly in a seemingly healthy person, may or may not have been witnessed, and was attributed to a cardiac cause after adjudication (as described in the Supplementary Appendix). Our definition of sudden cardiac arrest included persons who did not survive (defined previously as sudden cardiac death) as well as persons who were successfully resuscitated.

We defined a competitive sport as any organized or sanctioned sporting event that had been certified by an official, recognized sports association; persons who participated in a competitive sport could have been either professional or amateur athletes. We defined a noncompetitive sport as any form of a sport or recreational physical activity that was not formally organized or sanctioned. Out-of-hospital cardiac arrest was considered to be associated with a sport if the person was estimated to have exerted more than 3 metabolic equivalents (METs) during the activity in question and if the cardiac arrest occurred either during the activity or within 1 hour after the activity, during either competition or training.[15,16]

STUDY POPULATION

All cases of out-of-hospital cardiac arrest of presumed cardiac cause (according to the standardized Utstein criteria[17-19]), as well as cases that could have been the result of a sudden cardiac arrest event (e.g., drownings), that occurred among persons 12 to 45 years of age, that were attended by paramedics, that were treated or untreated (according to criteria specified by the medical directives of the EMS that define the presence or absence of signs of obvious death), and that resulted in death or in resuscitation were identified from the Rescu Epistry database from the beginning of 2009 to the end of 2014. The lower age limit for the study was chosen to include athletes who were potentially eligible for screening. The upper age limit was chosen to maximize the inclusion of persons who had heritable cardiac syndromes and to reduce overlap with out-of-hospital cardiac arrest due to atherosclerotic coronary artery disease.

The estimated total number of competitive athletes in the region served by the participating EMS agencies (Fig. S1 in the Supplementary Appendix) who were 12 to 45 years of age was calculated on the basis of the total number of competitive athletes who had registered with a sporting organization in Ontario during 2012 (information was obtained through direct correspondence with the Ontario Ministry of Tourism, Culture, and Sport) and was prorated according to the age-matched population in the geographic area covered by the study with the use of the 2011 Canadian Census. Athletes who were registered in racing events were recorded separately from those who participated in other sports, according to region and age group.[20] It was assumed that the number of athletes did not vary significantly from year to year within the study period.[21]

CASE IDENTIFICATION

Cases of out-of-hospital cardiac arrest that were related to competitive or noncompetitive sports were defined as cases that occurred during, or within 1 hour after, exertion of more than 3 METs during the activity. We identified such cases by manually sorting through all ambulance call reports and records from the emergency department or hospital for reports of persons who had a cardiac arrest at a recreational facility, university or college, sports field, stadium or arena, athletic facility, golf course, water area, hotel, condominium or apartment, park, or street.

Cases were cross-referenced by comparison with additional data sources to obtain a clinical and pathological assessment that was as complete as possible. The data sources that were used included ambulance call reports, fire call reports, in-hospital data (abstracted from emergency department reports, in-hospital medical notes, discharge summaries, consultations, clinical tests, and medical certificates of death),

medical records from family physicians, coroner investigative statements, autopsy reports, toxicology reports, and records of direct interviews with patients or family members. All out-of-hospital cardiac arrests were classified as either sudden cardiac arrest or cardiac arrest from other causes, as defined above and described previously.[22]

AUTOPSY AND MOLECULAR AUTOPSY

Autopsies were performed at the Provincial Forensic Pathology Unit of Ontario, which conducts approximately 6000 autopsies annually (Statistics Canada 2014, www.mcscs.jus.gov.on.ca/english/DeathInvestigations/Pathology/pathology_main.html), and were conducted either by forensic pathologists or by cardiovascular pathologists according to a standardized protocol in which all organs are examined both macroscopically and microscopically.[4] Criteria for identifying specific cardiac pathologies have been described previously[23]; additional details are provided in the Supplementary Appendix. Molecular autopsies, if performed, were done by analysis (GeneDx, Familion, or CTGT Connective Tissue Gene Tests) of DNA samples obtained from whole blood at the time of the autopsy.

STATISTICAL ANALYSIS

Descriptive statistics were used to assess the distribution of variables; continuous variables were summarized as mean values with standard deviations, and categorical variables were summarized as counts and percentages. Incidence rates per 100,000 person-years were calculated in the total population of competitive athletes over a 6-year period. All calculations and analyses were performed with the use of SPSS software, version 23.0 (IBM).

RESULTS

STUDY PARTICIPANTS AND DETAILS OF CARDIAC ARRESTS

The population of persons 12 to 45 years of age in the region served by the participating EMS agencies (Fig. S1 in the Supplementary Appendix) was estimated to be 3,085,240 in 2011. The estimated total follow-up time was 18.5 million person-years between the beginning of 2009 and the end of 2014. There were an estimated 352,499 registered competitive athletes in the study region in 2012 (which represented 11.4% of the population in the study region), resulting in an estimated total follow-up time of 2.1 million athlete-years. A total of 3825 out-of-hospital cardiac arrests among persons 12 to 45 years of age occurred during the study period, of which 2144 occurred in a public place. We reviewed the ambulance call reports for all 2144 cases, as well as the associated in-hospital records, coroner's records, and records of direct interviews with patients or family members, as appropriate. Of the cardiac arrests that occurred in a public place, 74 were determined to be sudden cardiac arrests that occurred during competitive sports (16 cases) or noncompetitive sports (58 cases) (Fig. 1).

Details of prehospital events and causes and outcomes of sudden cardiac arrest are provided in Table 1 for the 16 cases that occurred during competitive sports and in Table S1 in the Supplementary Appendix for the 58 cases that occurred during noncompetitive sports. Data sufficient to ascertain the cause of the sudden cardiac arrest among persons participating in competitive sports were obtained in 10 of the 16 cases. In 2 cases of nonsurvivors in which autopsies did not identify a cause of death, the cause of the sudden cardiac arrest was considered to be primary arrhythmia. In 4 cases of survivors in which no cause was identified after a detailed investigation, the cause of the cardiac arrest was also considered to be primary arrhythmia. In all 6 cases, either the cardiac structure was normal at autopsy or the results of the cardiac investigations, such as echocardiography or cardiac catheterization, were normal in the survivors.

RATES AND CAUSES OF SUDDEN CARDIAC ARREST

The sports associated with the greatest number of cases of sudden cardiac arrest among competitive athletes were race events and soccer (4 events each) (Table 2) and among noncompetitive athletes were gym workouts (12 events) and running (9 events) (Table S2 in the Supplementary Appendix). Assuming that all registered athletes are competitive athletes, the incidence of sudden cardiac arrest, including both survivors and nonsurvivors, during competition or training was 0.76 cases per 100,000 athlete-years (Table 3). Survival rates among competitive and noncompetitive athletes who had sudden cardiac

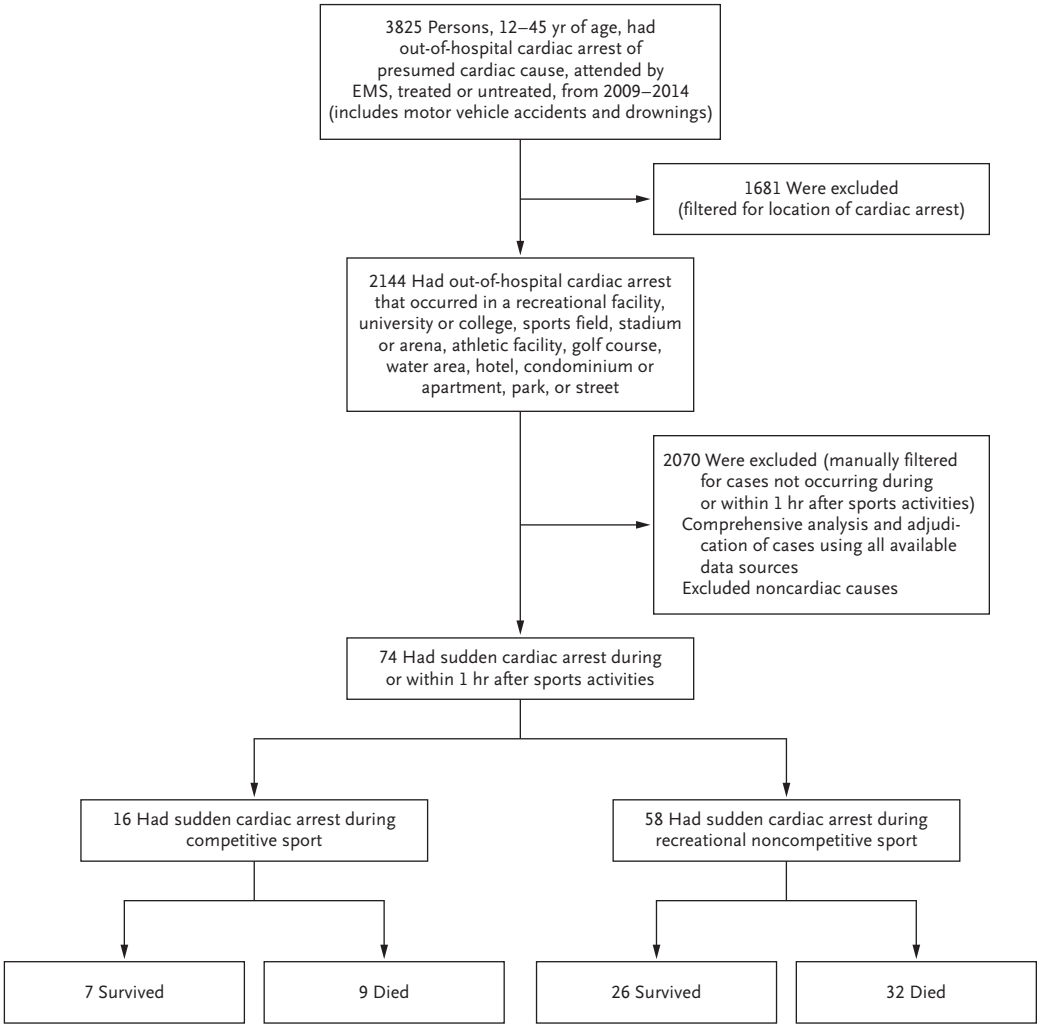

Figure 1. Identification and Classification of Out-of-Hospital Sudden Cardiac Arrest during Sports in Persons 12 to 45 Years of Age.

All 3825 out-of-hospital cardiac arrests that occurred among persons 12 to 45 years of age from 2009 through 2014 and were reported in the Rescu Epistry database were filtered on the basis of the type of location (e.g., a recreational facility) of the cardiac arrest. All 2144 remaining cases were then manually filtered for out-of-hospital cardiac arrests that occurred during or within 1 hour after a sports activity. This remaining cohort of 74 cases was assessed comprehensively with the use of all available records to adjudicate the cause of sudden cardiac arrest; cases of cardiac arrest due to noncardiac causes (e.g., hanging, trauma, mechanical suffocation, asphyxia from drowning, or toxic inhalation) were excluded from the assessment. EMS denotes emergency medical services.

arrest were similar (43.8% and 44.8%, respectively) (Table 4).

There were no significant differences in the distribution of causes of sudden cardiac arrest between survivors and nonsurvivors. The predominant cause of sudden cardiac arrest varied according to age group; among competitive and noncompetitive athletes younger than 35 years of age, structural and primary arrhythmic causes were the most common causes, whereas among persons 35 to 45 years of age, coronary artery disease was the most common cause (Table 4). Hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy were un-

Table 1. Details of Sudden Cardiac Arrest among Competitive Athletes.*

Patient No. (Sex, Age)	Bystander Witnessed; Performed CPR	EMS Response Time	Initial Cardiac Rhythm	No. of Shocks	Outcome	Autopsy	Molecular Autopsy	Cause of Sudden Cardiac Arrest	Basis of Diagnosis†	Previous Cardiac Tests	Follow-up
1 (M, 44 yr)	No; No	ND	VF/VT	1	Admitted to hospital; survived	NA	NA	Ischemic	Angiogram	ECG and echocardiogram normal	PCI and stents placed for coronary artery disease
2 (M, 30 yr)	Yes; Yes	ND	VF/VT	1	Admitted to hospital; survived	NA	NA	Primary arrhythmic	—	None	ECG, angiogram, stress test, and MRI normal; ICD implanted
3 (M, 16 yr)	Yes; Yes	6.5 min	VF/VT	2	Admitted to hospital; survived	NA	NA	Commotio cordis	History	None	In long-term care facility owing to anoxic brain injury
4 (F, 22 yr)	Yes; No	ND	PEA	0	Admitted to hospital; survived	NA	NA	Primary arrhythmic	—	None	ECG and echocardiogram normal; MRI showed possible myocarditis; ICD implanted
5 (M, 25 yr)	Yes; Yes	8.0 min	VF/VT	2	Admitted to hospital; survived	NA	NA	Primary arrhythmic	—	None	ECG, echocardiogram, and angiogram normal; ICD implanted
6 (M, 23 yr)	Yes; Yes	7.9 min	VF/VT	0	Admitted to hospital; survived	NA	NA	Primary arrhythmic	—	None	ECG abnormal‡; echocardiogram and MRI normal
7 (M, 13 yr)	Yes; Yes	5.4 min	VF/VT	0	Admitted to hospital; survived	NA	NA	Commotio cordis	History	None	ECG, echocardiogram, and stress test normal; incidental anomalous coronaries
8 (M, 35 yr)	Yes; Yes	9.5 min	VF/VT	1	Died in ED	Yes	NA	Ischemic	Autopsy	None	NA
9 (M, 18 yr)	Yes; Yes	11.0 min	Not shockable	3	Died in ED	Yes	No mutations detected	Primary arrhythmic	Normal autopsy	None	NA
10 (M, 27 yr)	Yes; No	4.8 min	Asystole	0	Died in ED	Yes	No mutations detected	Primary arrhythmic	Normal autopsy	None	NA
11 (M, 20 yr)	Yes; Yes	9.1 min	VF/VT	5	Died in ED	Yes	NA	Anomalous coronaries	Autopsy	Unknown	NA
12 (M, 15 yr)	Yes; No	5.2 min	VF/VT	5	Died in ED	Yes	Mutation (variant) of unknown significance§	Hypertrophic cardiomyopathy	Autopsy	ECG and echocardiogram normal	NA
13 (F, 18 yr)	Yes; Yes	7.0 min	PEA	0	Died in ED	Yes	NA	Anomalous coronaries	Autopsy	None	NA

14 (M, 39 yr)	Yes; Yes	ND	VF/VT	1	Died in ED	Yes	NA	Ischemic	Autopsy	None	NA
15 (M, 18 yr)	Yes; No	5.3 min	VF/VT	5	Admitted to hospital; died	No¶	NA	Hypertrophic cardiomyopathy	In-hospital testing	None	NA
16 (F, 12 yr)	Yes; Yes	ND	Not documented	0	Died in ED	Yes	NA	Anomalous coronaries	Autopsy	Previous investigations normal; cleared for competition	NA

* The specific type of sports activity in which each patient was participating is not specified to preserve patient confidentiality. CPR denotes cardiopulmonary resuscitation, ECG electrocardiogram, ED emergency department, EMS emergency medical services, ICD implantable cardioverter–defibrillator, MRI magnetic resonance imaging, NA not applicable, ND not documented, PCI percutaneous coronary intervention, PEA pulseless electrical activity, VF ventricular fibrillation, and VT ventricular tachycardia.
† A dash indicates no diagnosis.
‡ The patient had an abnormal electrocardiogram, with diffuse T wave inversions, but hypertrophic cardiomyopathy and long-QT syndrome were ruled out after expert consultation.
§ The mutation detected was *TNNI3* Arg141Gln.
¶ In-hospital investigations confirmed the diagnosis; therefore, an autopsy was deemed unnecessary.

common causes of sudden cardiac arrest. Hypertrophic cardiomyopathy was reported as the cause of sudden cardiac arrest in 12.5% of competitive athletes and in 6.9% of noncompetitive athletes, and arrhythmogenic right ventricular cardiomyopathy was identified as the cause of sudden cardiac arrests in none of the competitive athletes and in 6.9% of noncompetitive athletes (Table 1, and Table S1 in the Supplementary Appendix).

With respect to abnormalities that could potentially have been identified during preparticipation screening of competitive athletes, two athletes had a structural abnormality (i.e., hypertrophic cardiomyopathy) that was likely to be associated with an abnormal electrocardiogram or echocardiogram.[23,24] One of the two athletes had been assessed for presyncope, had a normal electrocardiogram and echocardiogram, was cleared to play competitive sports, and had hypertrophic cardiomyopathy that was diagnosed at autopsy (Patient 12 in Table 1). In addition, two of the competitive athletes who died had no structural abnormalities identified at autopsy, and therefore, the causes of sudden cardiac arrest in these athletes were classified as "primary arrhythmic" (Tables 1 and 4). If we assume that the athlete who had not previously undergone preparticipation screening and had hypertrophic cardiomyopathy had abnormalities that could have been identified by screening, and that the two athletes who died from causes classified as primary arrhythmic might have had a disorder that could have been detected while they were alive, we conclude that, at most, three of these persons could have been identified by preparticipation screening as being at risk for sudden cardiac arrest.

DISCUSSION

We used data on all out-of-hospital cardiac arrests attended by EMS personnel in a defined region of Ontario, Canada, to determine how frequently sudden cardiac arrest occurs among young persons during competitive and noncompetitive sports activities. Over the course of the 6-year study period, we identified 16 cases of sudden cardiac arrest that occurred during competitive sports and 58 cases of sudden cardiac arrest that occurred during noncompetitive sports. Hypertrophic cardiomyopathy and arrhythmo-

Table 2. Total Number of Sudden Cardiac Arrests among Competitive Athletes, According to Type of Sport.

Sport	Estimated No. of Athletes in 2012	Total Sudden Cardiac Arrests from 2009 through 2014
Race events*	73,382	4
Alpine skiing	1,793	0
Baseball	6,343	1
Basketball	9,668	2
Cycling	1,100	0
Gymnastics	3,551	0
Ice hockey	116,390	2
Jujitsu	1,230	2
Lacrosse	6,474	0
University or college team	20,485	0
Rugby	4,420	1
Soccer	11,265	4
Softball	3,394	0
Swimming	5,442	0
Tennis	1,569	0
Volleyball	4,065	0
All other registered sports†	81,928	0
Total	352,499	16

* This category includes events such as marathons, biathlons, triathlons, and obstacle course races.

† This category includes sports such as badminton, ball hockey, boxing, cross country running, curling, disc sports, diving, equestrian, fencing, field hockey, football, rowing, sailing, Special Olympics, table tennis, handball, water polo, weight lifting, wheelchair sports, and wrestling.

Table 3. Incidence of Sudden Cardiac Arrest among Competitive Athletes.

Variable	Age Group			
	12–17 yr	18–34 yr	35–45 yr	All
Athlete-years of observation from 2009 through 2014	342,600	1,036,974	735,420	2,114,994
No. of athletes who had sudden cardiac arrest	4	9	3	16
No. of cases per 100,000 athlete-yr	1.167	0.868	0.408	0.756

genic right ventricular cardiomyopathy were uncommon in our study population; among the 16 cases of sudden cardiac arrest that occurred during competitive sports, only 2 cases of hypertrophic cardiomyopathy and no cases of arrhythmogenic right ventricular cardiomyopathy were found. Our results indicate that sudden cardiac death during participation in competitive sports is rare, the causes are varied, and more than 80% of cases would not have been identified with the use of systematic clinical preparticipation screening alone or in combination with electrocardiography-based preparticipation screening.

The absolute incidence of sudden cardiac death (i.e., sudden cardiac arrest resulting in death) among athletes has previously been reported to be between 1 in 80,000 and 1 in 200,000 per year.[25,26] The incidence of sudden cardiac arrest during participation in competitive sports in our analysis (0.76 cases per 100,000 athlete-years) is similar to that reported previously[3,5] and includes resuscitated persons, which thus provides a more comprehensive estimate of the incidence. By comparison, the incidence of sudden cardiac arrest in the general population of the same age group has been reported to be 4.84 cases per 100,000 person-years.[22]

Previous studies suggest that hypertrophic cardiomyopathy accounts for a large proportion of sudden cardiac arrests during participation in competitive sports in contemporary North American populations.[27,28] In our cohort, however, hypertrophic cardiomyopathy was an uncommon cause of sudden cardiac arrest. Possible explanations for this unexpected lower rate include the wider age range in our study and genetic differences among populations in different geographic regions; however, a similarly low prevalence has also been reported by others.[4,29,30]

The rarity of sudden cardiac arrest due to structural heart disease that we found in our analysis raises questions about the potential value of preparticipation screening. Structural heart disease, such as hypertrophic cardiomyopathy, is more likely to be detected by electrocardiography than other causes of sudden cardiac arrest and is frequently cited as a reason for undertaking preparticipation screening.[31,32] In a French study[10] involving 6372 competitive athletes, 54 athletes (0.85%) were found to have hypertrophic cardiomyopathy, and all 54 athletes were disqualified from competition. If all the registered athletes in our jurisdiction had been screened, assuming the same prevalence, approximately 3000 athletes may have been identi-

fied as having hypertrophic cardiomyopathy and subsequently disqualified. Assuming a more widely quoted prevalence rate of 1 in 500 persons with hypertrophic cardiomyopathy in the general population,[33] 700 athletes with hypertrophic cardiomyopathy could have been disqualified from competition. In contrast, we identified 2 persons who had sudden cardiac arrest due to hypertrophic cardiomyopathy among competitive athletes during participation in sports activities, 1 of whom had undergone investigations for presyncope and was subsequently cleared for competition.

Among the survivors identified in our study, none had a condition that was likely to have been identified by preparticipation screening. Among the persons who died, our data suggest that systematic preparticipation screening may have identified a maximum of 3 persons who were at risk for sudden cardiac arrest. This conservative estimate assumes that screening would have identified abnormalities in the athlete with hypertrophic cardiomyopathy who had not previously undergone preparticipation screening and that the 2 athletes who died and had normal autopsy results had conditions that might have been identified by screening. In total, assuming that all these athletes could have been determined to be at risk for sudden cardiac arrest with the use of screening, at least 146,000 athletes would have had to be screened to identify 1 person who had sudden cardiac arrest during participation in competitive sports.

Table 4. Causes of Sudden Cardiac Arrest among Competitive and Noncompetitive Athletes, According to Age Group.

Variable	Age Group			
	12–17 yr	18–34 yr	35–45 yr	All
Competitive				
No. of athletes	4	9	3	16
Percent of athletes who survived	50.0	44.4	33.3	43.8
Diagnosis				
Ischemic*	0	0	3	3
Primary arrhythmic	0	6	0	6
Structural†	2	3	0	5
Commotio cordis	2	0	0	2
Noncompetitive				
No. of athletes	9	18	31	58
Percent of athletes who survived	66.7	50.0	35.5	44.8
Diagnosis				
Ischemic*	0	5	21	26
Primary arrhythmic	4	5	0	9
Unknown	2	2	0	4
Structural‡	3	6	8	17
Other§	0	0	2	2

* This diagnosis refers to coronary artery disease.
† This category includes hypertrophic cardiomyopathy and anomalous coronary arteries.
‡ This category includes hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, tetralogy of Fallot, and other cardiomyopathies.
§ This category includes aortic dissection and unspecified cardiac disease.

Our study has several important limitations. First, our analysis was a retrospective analysis, and the cause of death could not always be determined with certainty. We did not have autopsy data for all the persons in the study who died (although anatomical information was available from imaging or autopsy for all the competitive athletes). Second, it is possible that some athletes who had a risk of sudden cardiac arrest may have been identified through "case finding" (i.e., an athlete may have had symptoms or may have been referred for family assessment) and refrained from participation in sports activities, thereby removing themselves from the at-risk cohort of athletes. In addition, some professional athletes (a very small cohort) had already undergone screening. Third, we cannot exclude the possibility that some competitive athletes may have had cardiac arrest during participation in recreational sports and may subsequently have been reported as such (which would again have resulted in lowering the incidence of sudden cardiac arrest in the competitive-athlete group). It is also possible that athletes in the competitive cohort could have been counted more than once if they were registered in multiple sports associations with the Ontario Ministry of Tourism, Culture, and Sport. Fourth, we did not evaluate sudden cardiac arrest in competitive athletes either at rest or more than 1 hour after a sports activity. Finally, we cannot be certain that we have identified all competitive athletes; undercounting would have resulted in an underestimation of rates of sudden cardiac arrest.

In summary, we used data on out-of-hospital cardiac arrests to determine how frequently sudden cardiac arrest occurs during participation in

competitive and noncompetitive sports activities among young persons. Among competitive athletes, the incidence of sudden cardiac arrest was estimated to be 0.76 cases per 100,000 athlete-years. Sudden cardiac arrest due to structural heart disease occurred infrequently during competitive sports.

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