Timing of initiation of renal-replacement therapy in acute kidney injury

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Hôpitaux Universitaires de Genève	Claudia Heidegger; Aurelie Perret; Philippe Montillier; Frederic Sangla; Seigenthaller Neils; Aude De Watteville
UNITED KINGDOM	
Barking, Havering and Redbridge University Hospitals NHS Trust	Mandeep-Kaur Phull; Aparna George; Nauman Hussain; Tatiana Pogreban
Barnsley Hospital NHS Foundation Trust	Steve Lobaz; Alison Daniels; Mishell Cunningham; Deborah Kerr; Alice Nicholson
Buckinghamshire Healthcare NHS Trust	Pradeep Shanmugasundaram; Judith Abrams; Katarina Manso; Geraldine Hambrook; Elizabeth McKerrow; Juvy Salva; Stephen Foulkes
Cardiff and Vale University Health Board	Matthew Wise; Matt Morgan; Jenny Brooks; Jade Cole; Tracy Michelle Davies; Helen Hill; Emma Thomas
Chelsea and Westminster Hospital NHS Foundation Trust	Marcela Vizcaychipi; Behrad Baharlo; Jaime Carungcong; Patricia Costa; Laura Martins
East Kent NHS Trust	Ritoo Kapoor; Tracy Hazelton; Angela Moon; Janine Musselwhite
Golden Jubilee National Hospital, NHS Scotland	Ben Shelley; Philip McCall
Guy's and St. Thomas' NHS Foundation Trust	Marlies Ostermann; Gill Arbane; Aneta Bociek; Martina Marotti; Rosario Lim; Sara Campos; Neus Grau Novellas; Armando Cennamo; Andrew Slack; Duncan Wyncoll; Luigi Camporota; Simon Sparkes; Rosalinde Tilley

University Hairmyres Hospital, NHS Lanarkshire	Austin Rattray; Gayle Moreland; Jane Duffy; Elizabeth McGonigal
King's College Hospital NHS Foundation Trust	Philip Hopkins; Clare Finney; John Smith; Harriet Noble; Hayley Watson; Claire-Louise Harris; Emma Clarey; Eleanor Corcoran
Leeds Teaching Hospital NHS Foundation Trust	James Beck; Clare Howcroft; Nora Youngs; Elizabeth Wilby; Bethan Ogg
Lincoln County Hospital – United Lincolnshire Hospitals NHS Foundation Trust	Adam Wolverson; Sandra Lee; Susie Butler; Maryanne Okubanjo; Julia Hindle
Liverpool University Hospitals NHS Foundation Trust	Ingeborg Welters; Karen Williams; Emily Johnson; Julie Patrick-Heselton; David Shaw; Victoria Waugh
Milton Keynes University Hospital NHS Foundation Trust	Richard Stewart; Esther Mwaura; Lynn Wren; Louise Mew; Sara-Beth Sutherland; Jane Adderley
University Hospital Monklands, NHS Lanarkshire	Jim Ruddy; Margaret Harkins
NHS Grampian	Callum Kaye; Teresa Scott; Wendy Mitchell; Felicity Anderson; Fiona Willox
North Tees and Hartlepool Foundation NHS Trust	Vijay Jagannathan; Michele Clark; Sarah Purv
Nottingham University Hospital - Queen's Medical Centre	Andrew Sharman; Megan Meredith; Lucy Ryan; Louise Conner; Cecilia Peters; Dan Harvey
Queen Elizabeth Hospital - Lewisham and Greenwich NHS Trust	Ashraf Roshdy; Amy Collins
Queen Elizabeth University Hospital	Malcolm Sim; Steven Henderson
Royal Bournemouth & Christchurch Hospitals NHS Trust	Nigel Chee; Sally Pitts; Katie Bowman; Maria Dilawershah; Luke Vamplew; Elizabeth Howe
Royal Brompton and Harefield NHS Foundation Trust	Paula Rogers; Clara Hernandez; Clara Prendergast; Jane Benton; Alex Rosenberg
Royal Surrey County Hospital NHS Foundation Trust	Lui G. Forni; Alice Grant; Paula Carvelli
Sheffield Teaching Hospitals NHS Foundation Trust	Ajay Raithatha; Sarah Bird; Max Richardson; Matthew Needham; Claire Hirst
St. George’s University Hospitals NHS Foundation Trust	Jonathan Ball; Susannah Leaver; Luisa Howlett; Carlos Castro Delgado; Sarah Farnell-Ward; Helen Farrah; Geraldine Gray; Gipsy Joseph; Francesca Robinson
St. Helen's and Knowsley Teaching Hospitals NHS Trust	Ascanio Tridente; Clare Harrop; Karen Shuker
University Hospital Ayr, NHS Ayrshire & Arran	Derek McLaughlan; Judith Ramsey; Sharon Meehan
University Hospital Lewisham, Lewisham and Greenwich NHS Trust	Bernd Oliver Rose; Rosie Reece-Anthony; Babita Gurung
University Hospitals Birmingham NHS Foundation Trust	Tony Whitehouse; Catherine Snelson; Tonny Veenith; Andy Johnston; Lauren Cooper; Ron Carrera; Karen Ellis; Emma Fellows; Samanth Harkett; Colin Bergin; Elaine Spruce; Liesl Despy; Stephanie Goundry; Natalie Dooley; Tracy Mason; Amy Clark

University Hospitals Coventry and Warwickshire NHS Trust	Gemma Dignam; Geraldine Ward
Warwick Hospital, South Warwickshire NHS Trust	Ben Attwood; Penny Parsons; Sophie Mason
St. Richard's Hospital, Western Sussex Hospitals NHS Foundation Trust	Michael Margarson; Jenny Lord; Philip McGlone
Worthing Hospital, Western Sussex Hospitals NHS Foundation Trust	Luke E. Hodgson; Indra Chadbourn; Raquel Gomez; Jordi Margalef
York Teaching Hospital NHS Foundation Trust	Rinus Pretorius; Alexandra Hamshere; Joseph Carter; Hazel Cahill; Lia Grainger; Kate Howard; Greg Forshaw; Zoe Guy
UNITED STATES	
Mayo Clinic, Rochester	Kianoush B. Kashani; Robert C. Albright Jr.; Amy Amsbaugh; Anita Stoltenberg; Alexander S. Niven
Rhode Island Hospital	Matthew Lynch; AnnMarie O'Mara; Syed Naeem; Sairah Sharif; Joyce McKenney Goulart
The Miriam Hospital	Matthew Lynch; AnnMarie O'Mara; Syed Naeem; Sairah Sharif; Joyce McKenney Goulart
University of Alabama at Birmingham	Ashita Tolwani; Claretha Lyas; Laura Latta
University of Florida	Azra Bihorac; Haleh Hashemighouchani; Philip Efron; Matthew Ruppert; Julie Cupka; Sean Kiley; Joshua Carson; Peggy White; George Omalay; Sherry Brown; Laura Velez; Alina Marceron
University of Kentucky	Javier A. Neyra; Juan Carlos Aycinena; Madona Elias; Victor M. Ortiz-Soriano; Caroline Hauschild; Robert Dorfman

2. Endorsement and Funding:

The STARRT-AKI trial was endorsed by the Canadian Critical Care Trials Group (CCCTG), the Canadian Nephrology Trials Network (CNTN), the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG), the United Kingdom Critical Care Research Group (UKCCRG), the Irish Critical Care Clinical Trials Group/Network (ICC-CTG/N) and the European Society of Intensive Care Medicine (ESICM).

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The funding organizations and partners were not involved in the design, implementation or management of the trial. All analyses were undertaken independent of the funding organizations and partners. This manuscript was written by the Co-Chairs and the members of the Writing Committee and the decision to submit for publication was independent of the funding organizations and partners.

3. Data Management and Monitoring:

Database programming and data management took place at the central coordinating centre located at the Applied Health Research Centre (AHRC), Toronto, ON, Canada. A manual of operations and data dictionary that defined each data element to be collected was developed. (Available at: https://www.ualberta.ca/critical-care/research/current-research/starrtaki/documents) (Accessed February 4, 2020).

Several procedures were undertaken to ensure data quality:

- A site initiation visit, delivered in person or by webinar, was performed by the STARRT-AKI trial Co-Chairs (Sean M Bagshaw; Ron Wald) or their delegates for local research personnel (i.e., research coordinators and investigators) prior to study commencement.
- The coordinating centre regularly generated a series of data management reports to ensure data quality and completeness. All queries emanating from these reports were addressed by local investigators and research personnel.
- Remote monitoring and source data verification. This monitoring was performed to verify critical variables related to eligibility, informed consent, data completeness and primary and secondary outcomes and was performed in a random sample of 2 of the first 5 patients enrolled at each site and subsequently, for 10% of patients randomized at each site. This was performed in Austria, Belgium, Brazil, Canada, Finland, Germany, Ireland, Italy, and the United States.
- Onsite monitoring and source data verification. This monitoring was to verify critical variables related eligibility, informed consent, data completeness and primary and secondary outcomes. This was performed in Australia, China, France, New Zealand, Switzerland and the United Kingdom.
- Further email and teleconference communication supplemented data management and data monitoring activities.

  The detailed summary of the data management and monitoring plan is available at: https://www.ualberta.ca/critical-care/research/current-research/starrtaki/documents (Accessed February 4, 2020).

4. Data Sharing Statement:

The STARRT-AKI data sharing statement will generally align with the data sharing policy of The George Institute for Global Health (https://www.georgeinstitute.org/data-sharing-policy).

The STARRT-AKI Co-Chairs and Steering Committee support the view that research data generated from publicly-funded research should be made available for sharing to enhance public well-being, to maximize the potential knowledge gained, to reduce redundant research and to facilitate scientific discovery and innovation.

Data sharing will be for the purposes of medical research and under the auspices of the consent under which the data were originally gathered.

De-identified individual participant data collected during the STARRT-AKI trial will be shared beginning two years after the publication of the primary and secondary analyses, with no end date.

Data will be made available to qualified researchers who provide a detailed and methodologically sound proposal with specific aims that are clearly outlined.

To gain access, qualified researchers will need to sign a data sharing and access agreement and will need to confirm that data will only be used for the purpose for which data access was granted.

Proposals should be directed to the trial Co-Chairs via email: bagshaw@ualberta.ca and Ron.Wald@unityhealth.to.

5. Supplemental Tables:

Table S1: Results of the planned interim analyses.

Primary outcome (90-day mortality)	Date	Accelerated	Standard	Relative Risk (95% CI)	P-value
First interim analysis	Dec 21, 2017	146/369	152/371	0.97 (0.81 to 1.15)	0.70
Second interim analysis	Aug 20, 2018	307/732	308/720	0.98 (0.87 to 1.11)	0.75
Third interim analysis	Mar 29, 2019	460/1079	464/1072	0.98 (0.89 to 1.09)	0.76

Abbreviations: CI = confidence interval

Proportions are presented as number of patients with primary outcome (numerator)/total number of patients randomized (denominator). All analyses are unadjusted.

The first interim analysis was performed when 25% (740 patients) reached the 90-day outcome. The second interim analysis was performed when 50% (1452 patients) reached the 90-day outcome. The third interim analysis was performed when 75% (2151 patients) reached the 90-day outcome.

The O'Brien-Fleming stopping rule was used with negligible impact on the final type 1 error rate.

Table S2: Eligibility criteria.
Inclusion criteria are (all must be fulfilled):
1. Age ≥18 years on the day of eligibility screening
2. Admission to an intensive care unit
3. Evidence of kidney dysfunction: serum creatinine ≥100 µmol/L [1.13 mg/dL] [women] or ≥130 µmol/L [1.47 mg/dL] [men] based on last bloodwork available prior to screening that has not declined by >27 µmol/L [0.3 mg/dL] compared to the highest value recorded in the preceding 48 hours
4. Evidence of severe acute kidney injury based on at least ONE of the following three criteria: i) 2-fold increase in serum creatinine from baseline; OR ii) current serum creatinine is ≥354 µmol/L [4.0 mg/dL] with a minimum increase of 27 µmol/L [0.3 mg/dL] from the baseline serum creatinine; OR iii) urine output <6 mL/kg in the prior 12 hours
Exclusion criteria are (none may be present):
1. Potassium at time of screening >5.5 mmol/L
2. Bicarbonate at time of screening <15 mmol/L
3. Presence of a drug overdose or dialyzable toxin that necessitates renal-replacement therapy
4. Lack of commitment to provide renal-replacement therapy as part of philosophy of care
5. Receipt of any renal-replacement therapy in the preceding 2 months
6. Kidney transplant within the past 365 days
7. Known advanced chronic kidney disease defined by an estimated glomerular filtration rate (eGFR) <20 mL/min/1.73 m^2
8. Presence or strong clinical suspicion of renal obstruction, rapidly progressive glomerulonephritis, vasculitis, thrombotic microangiopathy or acute interstitial nephritis
If the patient fulfilled all *inclusion criteria* and none of the aforementioned *exclusion criteria* had been identified, the patient was deemed to be *provisionally eligible*. The next step was to ascertain whether the most responsible clinician(s) (the attending critical care physician and where relevant, the attending nephrologist) were in a position of clinical equipoise with respect to the two renal-replacement therapy initiation strategies that the provisionally eligible patient would receive if he/she was randomized. This was performed in practice by ascertaining the presence of the following two exclusion criteria:
9. Clinician(s) caring for patient believed that immediate renal-replacement therapy was mandated. After fulfilling the above inclusion/exclusion criteria, the study team was to speak to the ICU and/or nephrology attending physician and ask if he/she agreed with statement: “Renal-replacement therapy must be initiated immediately for this patient.” If the answer was “Yes”, the patient was excluded but could have been re-screened for eligibility, if applicable.
10. Clinician(s) caring for patient believed that deferral of renal-replacement therapy was mandated. After fulfilling the above inclusion/exclusion criteria, the study team was to speak to the ICU and/or nephrology attending physician and ask if he/she agreed with statement: “Renal-replacement therapy must be deferred for this patient.” If the answer was “Yes”, the patient was excluded, but could have been re-screened for eligibility.
A negative answer by all of the relevant clinicians to exclusions 9 and 10 formally transitioned the patient’s status from *provisional* to *full* eligibility. The time of full eligibility was noted and marked the beginning of a 12-hour period, during which informed consent must have been obtained (or alternate consent approaches invoked) and the patient randomized. If consent could not be secured during the 12 hours after full eligibility was established, the patient was no longer eligible for participation.

Table S3: Pre-planned exploratory analyses of death at 90-days (primary outcome) and renal-replacement therapy dependence at 90-days (secondary outcome).
Primary Outcome (Death at 90 days)
1. “Adjusted” analysis – We performed an adjusted logistic regression analysis of the primary outcome and report this as an adjusted-odds ratio (95% CI), adjusting for baseline characteristics (age, sex, baseline eGFR, Simplified Acute Physiology Score [SAPS] II score at enrollment, surgical admission, sepsis). Continuous variables (age, eGFR, SAPS II score) were modelled using restricted cubic splines with 4 knots to accommodate the possibility of non-linear relationships with the log-odds of death.
2. “As-Treated” population analysis – We analyzed the effect of the treatment strategy in an “as-treated” population, defined by analyzing patients according to the renal-replacement therapy initiation strategy that was delivered (e.g., patients allocated to the accelerated-strategy who did not receive renal-replacement therapy or started renal-replacement therapy beyond 12 hours from full eligibility were analyzed as “standard- strategy”; and patients allocated to the standard-strategy who started renal-replacement therapy within 12 hours of full eligibility were analyzed as “accelerated-strategy”).
3. Heterogeneity of treatment effect analysis – To assess for heterogeneity of treatment effect of the treatment-strategy on the primary outcome by illness acuity, death at 90-days was analyzed across baseline predicted risk of death using the SAPS II score, by use of an interaction term between treatment-strategy and SAPS II score in the fully adjusted model.
Secondary Outcome (Renal-replacement therapy dependence at 90-days)
The proportion of survivors who were renal-replacement therapy dependent at 90-days required special consideration, as the non-inclusion of patients who died may have obviated the intergroup balance afforded by randomization. We undertook two complementary approaches to address this.
1. Inverse probability weighting – We developed a logistic regression model for the primary outcome to estimate the probabilities of survival at 90-days. We then used the reciprocals of these probabilities as weights in a logistic regression analysis for renal-replacement therapy dependence at 90-days.
2. Multinomial regression – We developed a multi-nominal model to jointly consider the following states: dead at 90-days, alive at 90-days and receiving renal-replacement therapy, and alive at 90-days and free of renal-replacement therapy.

Table S4: Summary of reasons for exclusion of patients randomized and found to be non-eligible.

Randomized Non-Eligible	Total	Accelerated-Strategy	Standard-Strategy
Total	**50**	**31**	**19**
Did not fulfill all inclusion criteria	**32**	**21**	**11**
Met an exclusion criterion	**18**	**10**	**8**
Exclusion 1 (Serum potassium >5.5 mmol/L)	1	1	0
Exclusion 2 (Serum bicarbonate <15 mmol/L)	9	5	4
Exclusion 3 (Drug overdose or toxin)	0	--	--
Exclusion 4 (Lack of commitment to RRT)	0	--	--
Exclusion 5 (Any RRT within prior 2 months)	1	0	1
Exclusion 6 (Kidney transplant within prior year)	0	--	--
Exclusion 7 (Advanced chronic kidney disease)	4	2	2
Exclusion 8 (Obstruction, GN, vasculitis, TMA)	3	2	1

Abbreviations: RRT = renal-replacement therapy GN = glomerulonephritis; TMA = thrombotic microangiopathy

Table S5: Expanded baseline characteristics by allocated treatment-strategy.

Characteristic	Accelerated-strategy	Data available	Standard-strategy	Data available
Age – yr	64.6 ± 14.3	1465	64.7 ± 13.4	1462
Female sex – no. (%)	470 (32.1)	1465	467 (31.9)	1462
Weight – kg	88.0 ± 27.4	1461	88.0 ± 25.1	1459
Baseline serum creatinine[a] – mg/dl	1.4 ± 1.0	1465	1.3 ± 1.0	1462
Baseline eGFR[b] – mL/min/1.73m^2	66.0 ± 29.8	1465	67.3 ± 29.8	1462
Clinical Frailty Scale score	3 (2 to 5)	1163	3 (2 to 5)	1142
Clinical Frailty Scale score > 4 – no. (%)	308 (26.5)	1163	308 (27.0)	1142
EQ-VAS	59.0 ± 26.7	756	60.4 ± 26.1	738
Pre-existing conditions – no. (%)				
Chronic kidney disease – (eGFR <60 mL/min/1.73m^2)	658 (44.9)	1465	626 (42.8)	1462
eGFR – mL/min/1.73m^2		1465		1462
≥ 60	807 (55.1)		836 (57.2)	
45-59	257 (17.5)		260 (17.8)	
30-44	230 (15.7)		183 (12.5)	
< 30	171 (11.7)		183 (12.5)	
Hypertension	814 (55.6)	1465	823 (56.3)	1461
Diabetes mellitus	439 (30.0)	1465	459 (31.4)	1462
Heart failure	204 (13.9)	1465	204 (14.0)	1461
Coronary artery disease	320 (21.8)	1465	328 (22.5)	1461
Liver disease	172 (11.7)	1465	165 (11.3)	1461
Metastatic cancer	77 (5.3)	1465	84 (5.7)	1462
Hematologic malignancy	87 (5.9)	1465	83 (5.7)	1462
HIV/AIDS	13 (0.9)	1465	13 (0.9)	1462
Admission category – no. (%)		1465		1462
Scheduled surgery	207 (14.1)		184 (12.6)	
Unscheduled surgery	285 (19.5)		289 (19.8)	
Medical	973 (66.4)		989 (67.6)	
Hospital-acquired risk factors for AKI in preceding 7 days – no. (%)				
Cardiopulmonary bypass	112 (7.6)	1465	118 (8.1)	1462
Aortic aneurysm repair	71 (4.8)	1465	74 (5.1)	1461
Other vascular surgery	76 (5.2)	1465	77 (5.3)	1462
Major trauma	62 (4.2)	1465	55 (3.8)	1462
Obstetric complications	5 (0.3)	1465	5 (0.3)	1462
Radiocontrast exposure	382 (26.1)	1463	375 (25.7)	1460
Receipt of an aminoglycoside	154 (10.5)	1463	148 (10.2)	1458
Receipt of amphotericin B	9 (0.6)	1464	12 (0.8)	1460
Characteristics at enrollment				
Sepsis – no. (%)	855 (58.4)	1465	834 (57.0)	1462
Septic Shock – no. (%)	640 (43.7)	1465	643 (44.0)	1462
SAPS II score[c]	58.1 ± 17.4	1465	59.4 ± 17.4	1462
SOFA score[d]	11.6 ± 3.6	1465	11.8 ± 3.6	1462
Physiological support and interventions – no. (%)				

Mechanical ventilation	1103 (75.3)	1465	1148 (78.5)	1462
Vasoactive support	1008 (68.8)	1465	1052 (72.0)	1462
Diuretic therapy	502 (34.3)	1465	508 (34.8)	1461
Enteral nutrition	525 (35.8)	1465	559 (38.2)	1462
Total parenteral nutrition	182 (12.4)	1465	167 (11.4)	1462
Physiological parameters				
Heart rate – beats/min	107 ± 27	1463	108 ± 26	1459
Systolic blood pressure – mmHg	102 ± 28	1462	101 ± 28	1457
Temperature – degrees Celsius	37.4 ± 1.3	1458	37.5 ± 1.4	1458
Glasgow coma scale	9.2 ± 4.9	1432	8.8 ± 5.0	1417
Urine output – mL/24hr	450 (190 to 945)	1415	478 (187 to 975)	1420
Oliguria or anuria[e]– no. (%)	647 (45.7)	1415	618 (43.5)	1420
Cumulative fluid balance[f] – mL	2581 (820 to 5362)	1378	2819 (836 to 5603)	1360
Percent Fluid overload[g] – no. (%)	3.1 (1.0 to 6.6)	1374	3.2 (0.9 to 6.8)	1357
Laboratory parameters				
Hemoglobin – g/dL	10.0 ± 2.3	1457	10.0 ± 3.0	1451
White blood cell count – cells x 10^9/L	18.4 ± 20.6	1455	17.8 ± 17.4	1444
Platelets – cells x 10^9/L	175 ± 122	1455	168 ± 115	1450
Serum bilirubin – mg/dL	2.6 ± 5.2	1269	2.4 ± 4.3	1277
Arterial pH	7.3 ± 0.1	1367	7.3 ± 0.1	1350
Serum sodium – mmol/L	138 ± 7	1465	138 ± 7	1460
Serum creatinine – mg/dL	3.6 ± 1.7	1464	3.4 ± 1.6	1461
Serum potassium – mmol/L	4.5 ± 0.8	1464	4.5 ± 0.8	1461
Serum bicarbonate – mmol/L	19.7 ± 4.7	1437	19.5 ± 4.5	1423
Blood urea nitrogen – mg/dL	60.8 ± 34.3	1382	61.0 ± 33.9	1380

Data are presented as mean ± standard deviation, median (interquartile range) or number (%).

Abbreviations: eGFR = estimated glomerular filtration rate; EQ-VAS = EuroQoL visual analogue scale; HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome; AKI = acute kidney injury; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment; TPN = total parenteral nutrition.

Data are presented as mean ± standard deviation, median (interquartile range) or number (%).

[a] Baseline serum creatinine was defined as the most recent outpatient serum creatinine obtained during the year preceding the current hospitalization. If this value was not available, the lowest serum creatinine during the current hospitalization was used to establish the baseline serum creatinine.
[b] Baseline eGFR was derived using the Chronic Kidney Disease - Epidemiology equation which incorporates the baseline serum creatinine, age, sex and whether the patient was of African background.
[c] Scores on the SAPS II score range from 0 to 163, with higher scores indicating more severe disease and a higher risk of death.
[d] Scores on the SOFA score range from 0-24, with higher scores indicating more severe disease and a higher risk of death.
[e] Oliguria was defined as urine output <400 mL/24hr. Data expressed as a proportion of patients with urine output available.
[f] Cumulative fluid balance from ICU admission.
[g] Fluid overload defined as cumulative fluid balance from ICU admission divided by earliest recorded weight during the hospitalization times 100 and expressed as a percentage.

Table S6: Characteristics at renal-replacement therapy initiation.

	Accelerated-strategy (N=1418)	Patients with available data	Standard-strategy (N=903)	Patients with available data
Time from eligibility to RRT initiation – hours	6.1 (3.9 to 8.8)	1417	31.1 (19.0 to 71.8)	903
Time from randomization to RRT initiation – hours	4.4 (2.7 to 6.6)	1417	29.1 (17.3 to 68.4)	903
Physiological parameters at RRT initiation				
Heart rate – beats/min	94 ± 21	1415	93 ± 20	898
Systolic blood pressure - mmHg	118 ± 23	1414	119 ± 23	897
Respiratory rate – breaths/min	21 ± 7	1410	22 ± 7	894
PaO_2/FiO_2 ratio	243 ± 110	1375	232 ± 113	873
Urine output in the preceding 24 hours – mL	453 (190 to 973)	1384	350 (100 to 1000)	889
Fluid balance – mL	2714 (872 to 5659)	1328	5893 (2265 to 11068)	829
Laboratory parameters at RRT initiation				
Serum creatinine – mg/dL	3.7 ± 1.7	1414	4.9 ± 2.1	900
Blood urea nitrogen – mg/dL	63.7 ± 49.8	1356	85.3 ± 51.3	869
Serum potassium – mmol/L	4.4 ± 0.7	1409	4.6 ± 0.8	903
Serum bicarbonate – mmol/L	20.6 ± 4.4	1388	19.5 ± 4.7	888
Arterial pH	7.3 ± 0.1	1335	7.3 ± 0.1	843
Hemoglobin – g/dL	9.9 ± 2.2	1399	9.3 ± 1.8	899
SOFA score at RRT initiation	10.9 ± 3.6	1417	12.1 ± 3.6	903
Presence of ≥ 1 Indication for RRT at time of RRT initiation in the standard arm – no. (%)	-		597 (66.1)	
Serum potassium ≥ 6 mmol/L – no. (%)			48 (5.3)	
pH ≤ 7.2 or Bicarbonate ≤ 12 mmol/L – no. (%)	-		150 (16.6)	
PaO_2/FiO_2 ≤ 200 and clinical perception of volume overload – no. (%)	-		394 (43.6)	
Time from randomization to RRT ≥ 72hrs – no. (%)	-		214 (23.7)	

Data are presented as mean ± standard deviation, median (interquartile range) or number (%).

Abbreviations: RRT = renal replacement therapy; AKI = acute kidney injury; SOFA = sequential organ failure assessment.

Table S7: Characteristics of the initial renal-replacement therapy prescription.

Characteristic	Accelerated-strategy (N=1418)	Patients with available data	Standard-strategy (N=903)	Patients with available data
RRT modality – no. (%)		1417		880
CRRT	969 (68.4)		621 (70.6)	
IHD	383 (27.0)		223 (25.3)	
SLED	65 (4.6)		36 (4.1)	
Dialysis catheter insertion site – no. (%)		1365		841
Jugular	805 (59.0)		488 (58.0)	
Femoral	519 (38.0)		332 (39.5)	
Subclavian	41 (3.0)		21 (2.5)	
Intermittent RRT duration prescribed				
IHD – hours	4.0 (3.0 to 4.0)	382	4.0 (2.6 to 4.0)	222
SLED – hours	8.0 (6.0 to 8.0)	65	8.0 (7.3 to 8.0)	36
CRRT dose prescribed – mL/kg/hr	28.3 (23.0 to 33.0)	963	28.6 (23.0 to 33.1)	619
Anticoagulation – no. (%)		1417		880
Citrate	639 (45.1)		383 (43.5)	
Heparin	407 (28.7)		260 (29.5)	
None	338 (23.9)		213 (24.2)	
Other	33 (2.3)		24 (2.7)	
Ultrafiltration achieved during first RRT session – mL	360 (0 to 1290)	1389	860 (50 to 2000)	867

Data are presented as mean ± standard deviation, median (interquartile range) or number (%).

Abbreviations: RRT = renal replacement therapy; IHD = intermittent hemodialysis; SLED = slow low efficiency dialysis; CRRT = continuous renal replacement therapy

Table S8: Summary of pre-planned inverse probability weighted and multinomial analyses for renal-replacement therapy dependence at 90-days.		
Analysis[a]	**Odds Ratio**	**95% CI**
Renal-replacement therapy-dependence at 90-days		
Unadjusted unweighted	1.82	1.26 to 2.63
Unadjusted weighted	1.71	1.31 to 2.24
Adjusted[b] weighted (IPW)	1.75	1.33 to 2.30
Multinomial analysis comparing accelerated versus standard strategies for each state		
Alive not renal-replacement therapy dependent	-	-
Alive and renal-replacement therapy dependent	1.82	1.26 to 2.63
Dead	1.05	0.90 to 1.22

Abbreviations: CI = confidence interval; IPW = inverse probability weighting

[a] Referent group are patients randomized to the standard RRT initiation strategy.

[b] Adjusted for age, sex, baseline eGFR, SAPS II score, surgical status and sepsis.

Table S9: Causes of death[a].

Cause	Accelerated-strategy (N=640)	Standard-strategy (N=630)
Neurological – no. (%)		
Brain death	6 (0.9)	8 (1.3)
Hypoxic encephalopathy	12 (1.9)	16 (2.5)
Intracranial hemorrhage	6 (0.9)	3 (0.5)
Ischemic stroke	8 (1.3)	4 (0.6)
Other	9 (1.4)	8 (1.3)
Cardiovascular – no. (%)		
Primary arrhythmia	30 (4.7)	28 (4.5)
Refractory cardiogenic shock	34 (5.3)	36 (5.7)
Cardiac tamponade	3 (0.5)	3 (0.5)
Hypovolemia (bleeding)	17 (2.7)	13 (2.1)
Septic shock	195 (30.5)	176 (28.0)
Massive pulmonary embolism	5 (0.8)	1 (0.2)
Anaphylaxis	1 (0.2)	1 (0.2)
Other	114 (17.8)	110 (17.5)
Respiratory – no. (%)		
Refractory hypoxia due to ARDS	40 (6.3)	46 (7.3)
COPD	6 (0.9)	9 (1.4)
Asthma	0	2 (0.3)
Pulmonary hemorrhage	0	2 (0.3)
Pneumothorax	2 (0.3)	0
Other	86 (13.4)	82 (13.0)
Metabolic – no. (%)		
Hypoglycemia	0	0
Hyperkalemia	0	4 (0.6)
Hypothermia	0	0
Liver failure	22 (3.4)	24 (3.8)
Other	44 (6.9)	54 (8.6)

Abbreviations: ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease.

[a] Cause of death not available for 12 patients, 3 patients in the accelerated-strategy and 9 patients in the standard-strategy.

Data were available on withdrawal of life-sustaining therapy for 1270/1282 patients (99.1%) who died: 412 (64.4%) in the accelerated-strategy and 391 (61.2%) in the standard-strategy.

Table S10. All-cause mortality at 90-days across pre-specified subgroups.

	Accelerated-strategy no. deaths/total	Standard-strategy no. deaths/total	Odds Ratio (95% CI)
Total Population	643/1465	639/1462	1.01 (0.87 to 1.17)
Patient sex			
Female	191/470	207/467	0.91 (0.69 to1.20)
Male	452/995	432/995	1.12 (0.93 to 1.36)
Patients with eGFR < 45 ml/min/1.73m^2			
Yes	184/401	150/365	1.26 (0.93 to 1.71)
No	459/1064	489/1097	0.99 (0.82 to 1.18)
Patients with SAPS II score > 58			
Yes	387/701	403/751	1.08 (0.87 to 1.34)
No	256/764	236/711	1.02 (0.81 to 1.28)
Patient surgical status			
Medical	458/973	483/989	0.99 (0.82 to 1.19)
Surgical	185/492	156/473	1.20 (0.91 to 1.59)
Patients with sepsis			
Yes	392/855	402/834	0.95 (0.78 to 1.17)
No	251/610	237/628	1.21 (0.95 to 1.54)
Geographic region			
North America	231/497	225/497	1.08 (0.83, to1.42)
Europe	254/574	260/572	1.00 (0.78 to 1.29)
Australia/New Zealand	91/275	86/278	1.12 (0.77 to 1.64)
Asia/South America	67/119	68/115	0.94 (0.53 to 1.68)

Abbreviations: GFR = glomerular filtration rate; SAPS = Simplified Acute Physiology Score.

Table S11. All-cause mortality at 90-days across participating countries.

Country (no. sites)	Accelerated-strategy (N=1465) no. deaths (%)	Standard-strategy (N=1462) no. deaths (%)	Odds Ratio (95% CI)
Total Population	643 (43.9)	639 (43.7)	1.01 (0.87 to 1.17)
Australia (16)			
Yes	63 (32.6)	59 (29.8)	1.15 (0.73 to 1.80)
No	580 (45.6)	580 (45.9)	1.04 (0.88 to 1.22)
Austria (4)			
Yes	16 (61.5)	10 (40.0)	2.88 (0.85 to 9.73)
No	627 (43.6)	629 (43.8)	1.03 (0.88 to 1.21)
Belgium (1)			
Yes	13 (59.1)	9 (39.1)	2.89 (0.82 to 10.24)
No	630 (43.7)	630 (43.8)	1.04 (0.89 to 1.21)
Brazil (1)			
Yes	4 (100)	2 (50)	-
No	639 (43.7)	637 (43.7)	1.05 (0.90 to 1.23)
Canada (43)			
Yes	195 (44.9)	191 (43.7)	1.08 (0.82 to 1.44)
No	448 (43.5)	448 (43.7)	1.04 (0.86 to 1.25)
China (14)			
Yes	63 (54.8)	66 (59.5)	0.90 (0.50 to 1.61)
No	580 (43.0)	573 (42.4)	1.06 (0.90 to 1.25)
Finland (3)			
Yes	4 (16.0)	7 (26.9)	0.50 (0.12 to 2.05)
No	639 (44.4)	632 (44.0)	1.06 (0.91 to 1.2)

France (29)			
Yes	176 (47.4)	191 (50.8)	0.88 (0.65 to 1.20)
No	467 (42.7)	448 (41.3)	1.12 (0.94 to 1.35)
Germany (2)			
Yes	9 (60.0)	6 (42.9)	2.89 (0.59 to 14.27)
No	634 (43.7)	633 (43.7)	1.04 (0.89 to 1.22)
Ireland (1)			
Yes	0	0	-
No	643 (43.7)	639 (43.7)	1.05 (0.90 to 1.23)
Italy (2)			
Yes	1 (100)	1 (50)	-
No	642 (43.9)	638 (43.7)	1.05 (0.90 to 1.23)
New Zealand (9)			
Yes	28 (34.1)	27 (33.8)	1.02 (0.51 to 2.02)
No	615 (44.5)	612 (44.3)	1.06 (0.90 to 1.24)
Switzerland (2)			
Yes	7 (35.0)	8 (44.4)	0.76 (0.19 to 2.98)
No	636 (44.0)	631 (43.7)	1.06 (0.90 to 1.24)
United Kingdom (35)			
Yes	28 (30.4)	28 (32.2)	1.11 (0.57 to 2.14)
No	615 (44.8)	611 (44.4)	1.05 (0.90 to 1.23)
United States (6)			
Yes	36 (57.1)	34 (56.7)	1.03 (0.48 to 2.20)
No	607 (43.3)	605 (43.2)	1.05 (0.90 to 1.24)

6. Supplemental Figures:

Figure S1: Screening and recruitment algorithm.

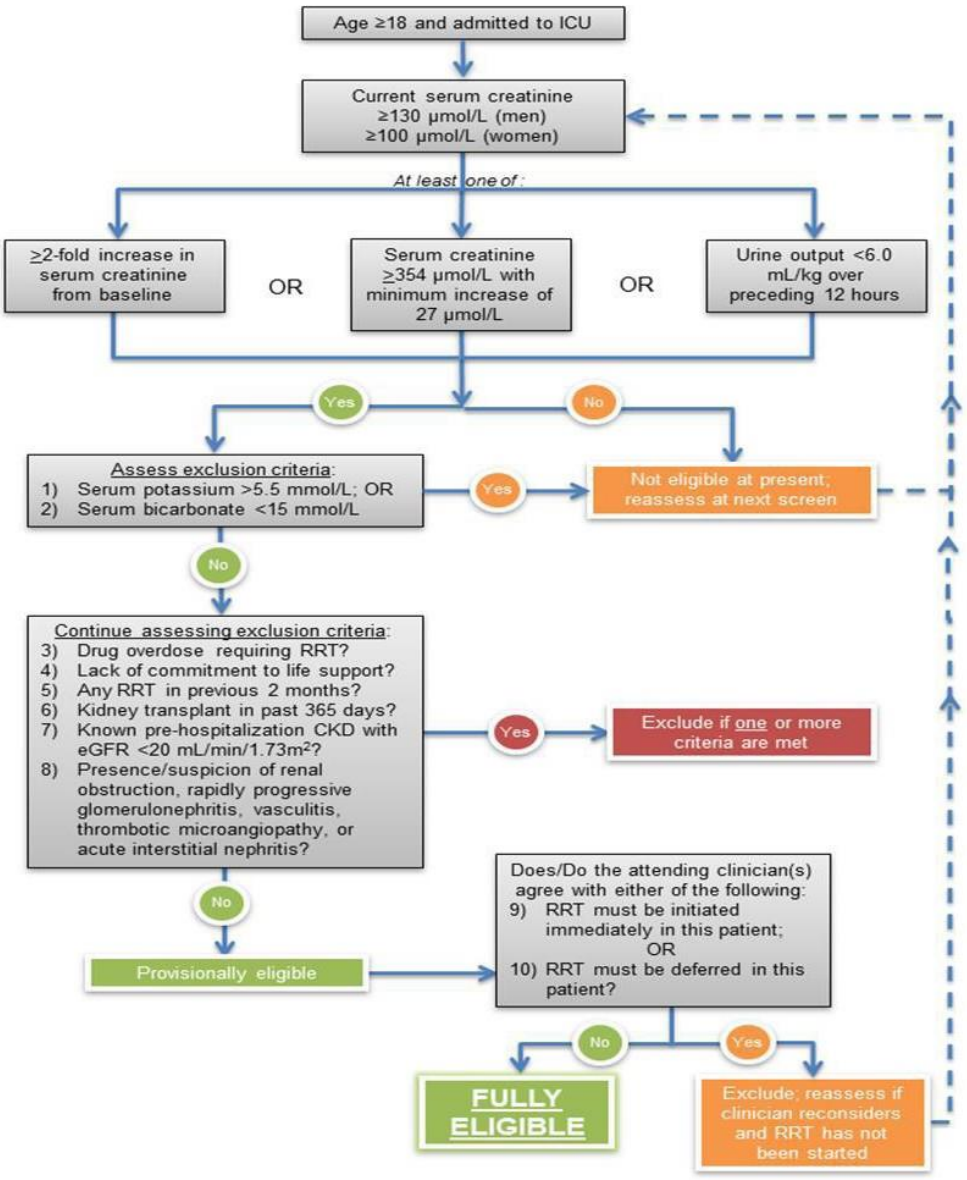
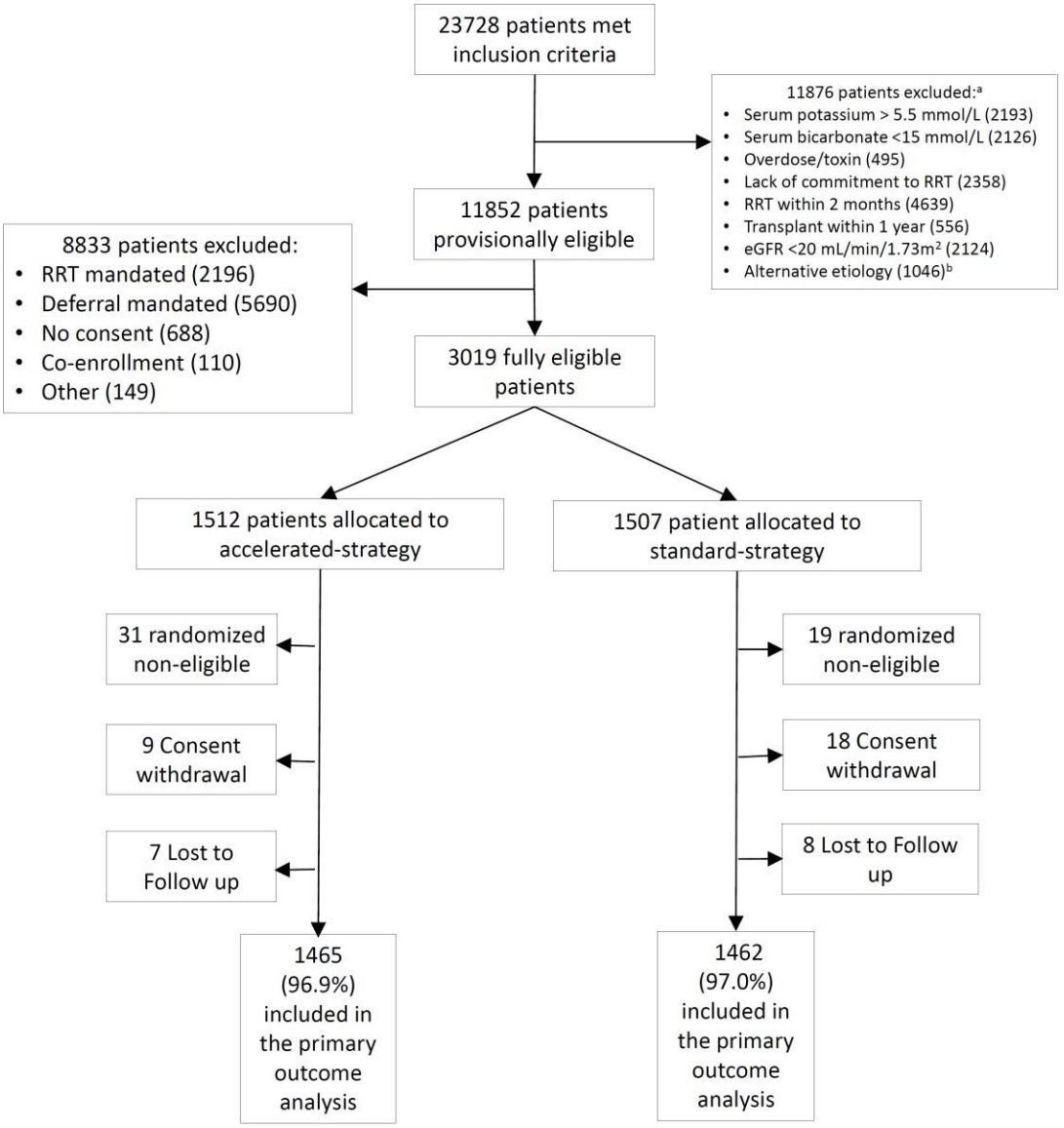


Figure S2. Participant flow diagram.



Legend:

[a] Excluded patients may have met more than 1 criterion.

[b] Confirmed or suspicion of alternative etiology for acute kidney injury such as obstruction, glomerulonephritis, vasculitis, thrombotic microangiopathy.

Figure S3: Time to renal-replacement therapy initiation accounting for the competing risk of death.

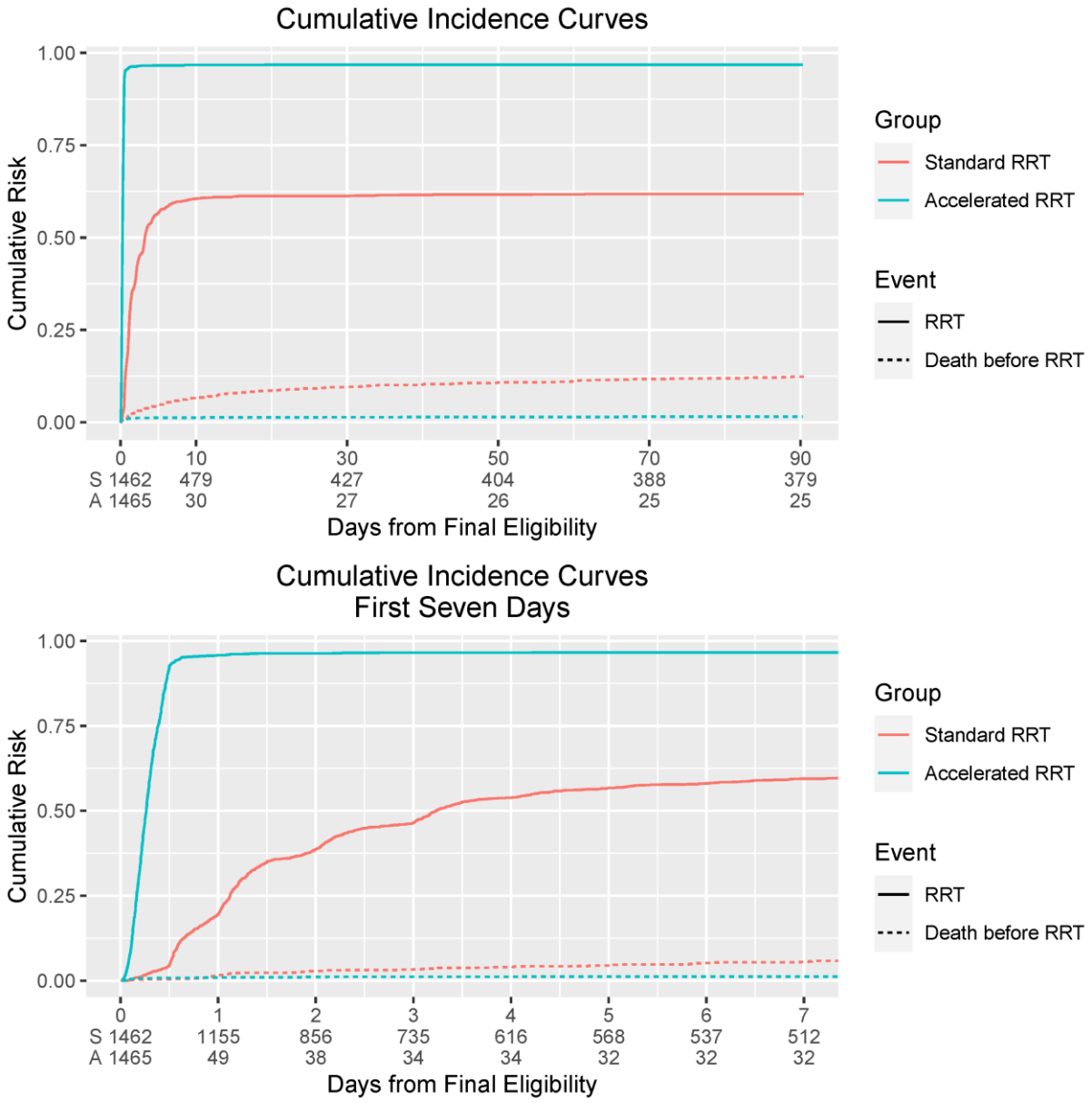


Figure S4: Kaplan-Meier survival estimates of the probability of survival to 90-days including patients lost to follow-up.

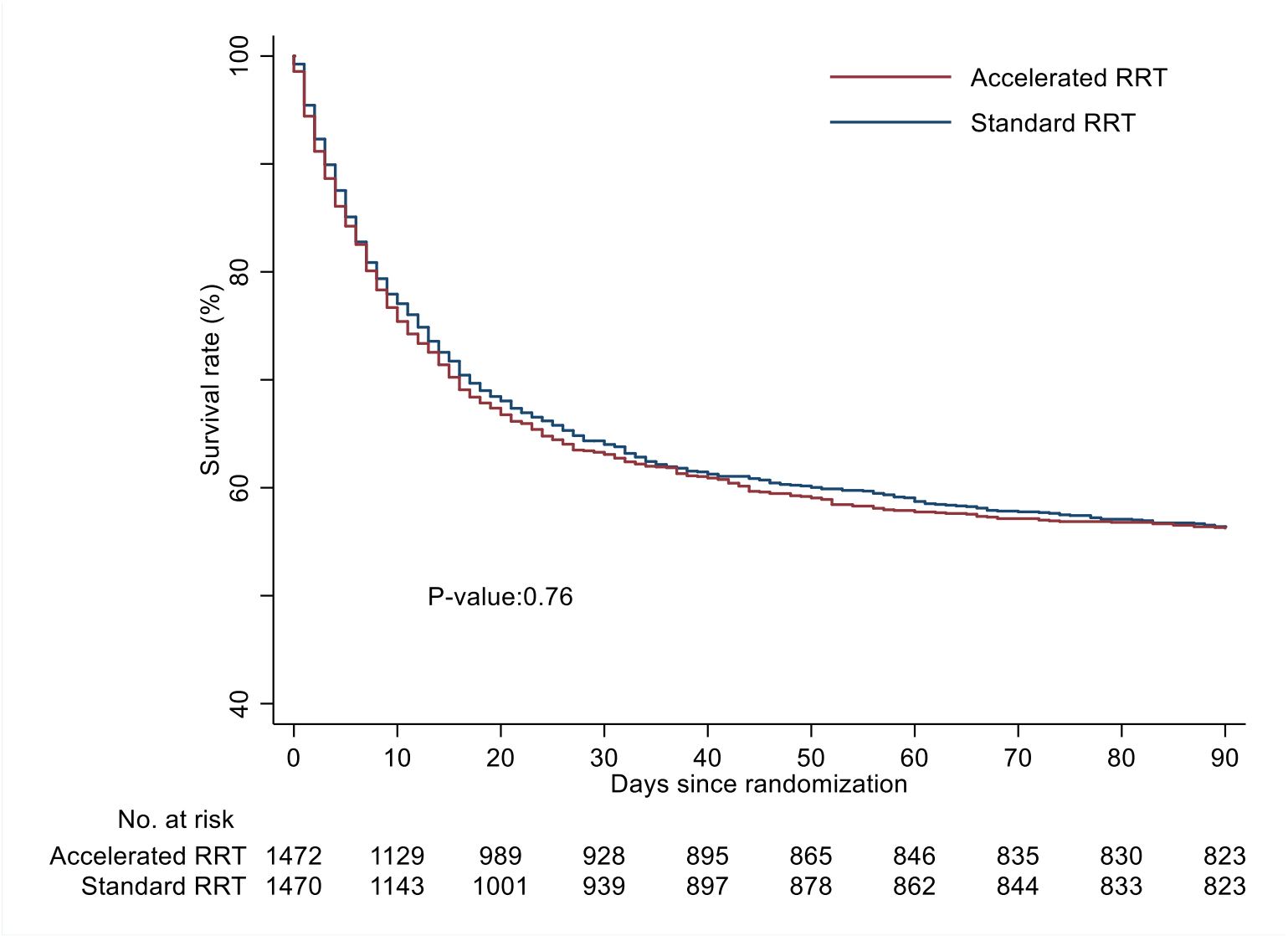


Figure S5. Heterogeneity of treatment effect by deciles of SAPS II score in fully adjusted model.