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A Bayesian reanalysis of the Standard versus Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial

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Abstract

Background: Timing of initiation of kidney-replacement therapy (KRT) in critically ill patients remains controversial. The *Standard versus Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury* (STARRT-AKI) trial compared two strategies of KRT initiation (accelerated versus standard) in critically ill patients with acute kidney injury and found neutral results for 90-day all-cause mortality. Probabilistic exploration of the trial endpoints may enable greater understanding of the trial findings. We aimed to perform a reanalysis using a Bayesian framework.

Methods: We performed a secondary analysis of all 2927 patients randomized in multi-national STARRT-AKI trial, performed at 168 centers in 15 countries. The primary endpoint, 90-day all-cause mortality, was evaluated using hierarchical Bayesian logistic regression. A spectrum of priors includes optimistic, neutral, and pessimistic priors, along with priors informed from earlier clinical trials. Secondary endpoints (KRT-free days and hospital-free days) were assessed using zero–one inflated beta regression.

Results: The posterior probability of benefit comparing an accelerated versus a standard KRT initiation strategy for the primary endpoint suggested no important difference, regardless of the prior used (absolute difference of 0.13% [95% credible interval [CrI] – 3.30%; 3.40%], – 0.39% [95% CrI – 3.46%; 3.00%], and 0.64% [95% CrI – 2.53%; 3.88%] for neutral, optimistic, and pessimistic priors, respectively). There was a very low probability that the effect size was equal or larger than a consensus-defined minimal clinically important difference. Patients allocated to the accelerated strategy had a lower number of KRT-free days (median absolute difference of – 3.55 days [95% CrI – 6.38; – 0.48]), with a probability that the accelerated strategy was associated with more KRT-free days of 0.008. Hospital-free days were similar between strategies, with the accelerated strategy having a median absolute difference of 0.48 more hospital-free days (95% CrI – 1.87; 2.72) compared with the standard strategy and the probability that the accelerated strategy had more hospital-free days was 0.66.

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Conclusions: In a Bayesian reanalysis of the STARRT-AKI trial, we found very low probability that an accelerated strategy has clinically important benefits compared with the standard strategy. Patients receiving the accelerated strategy probably have fewer days alive and KRT-free. These findings do not support the adoption of an accelerated strategy of KRT initiation.

Keywords: Bayesian, Kidney-replacement therapy, Acute kidney injury, Mortality, Dialysis, Randomized, Trial

Background

Timing of kidney replacement therapy (KRT) initiation in critically ill patients with severe acute kidney injury (AKI) is controversial and has been the focus of several recent randomized trials [1–4]. These trials have been driven by the premise that earlier KRT can facilitate more rapid correction of metabolic, acid–base, and fluid balance derangements, prevent AKI-related complications, and improve clinical outcomes [5–7]. At the same time, KRT is also recognized as an invasive and resource-intensive intervention associated with risks, such as placement of a large central venous catheter, exposure to an extracorporeal circulation, and therapy-related complications, in particular episodes of hemodynamic instability, which may modify the probability of kidney recovery and independence from KRT [2, 3, 8].

The *Standard versus Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury* (STARRT-AKI) trial found no important difference in the primary endpoint of 90-day all-cause mortality when comparing the accelerated with the more conservative strategy for starting KRT in critically ill patients with severe AKI; however, the accelerated strategy conferred greater risk for KRT dependence at 90 days among hospital survivors [3]. The STARRT-AKI trial was designed as a frequentist trial and was interpreted using a traditional framework of null hypothesis testing with a dichotomous interpretation of p values under a Neyman–Pearson concept [9]. The reinterpretation of the STARRT-AKI trial through a Bayesian framework may align more naturally with clinician decision-making and provide a more straightforward context, including the provision of direct probabilities of benefit or harm, probabilities of the effect size being within a range of relevant effect sizes, and estimates of equivalence [10–12].

Accordingly, we performed a secondary post hoc analysis of the STARRT-AKI trial data under a Bayesian framework, focusing on assessing the effect of accelerated compared with standard KRT initiation on 90-day all-cause mortality and, secondly, on key kidney-specific outcomes.

Methods

Aim, Design and Setting We performed a post hoc secondary analysis of the STARRT-AKI trial (Data Creation Plan available at: <https://www.ualberta.ca/critical-care/research/current-research/starrtaki/documents.html>) [3, 13, 14]. In brief, the STARRT-AKI trial randomized critically ill patients greater than 18 years old with kidney dysfunction (serum creatinine level ≥ 1.13 mg per deciliter [$100 \mu\text{mol/l}$] in women and ≥ 1.47 mg per deciliter [$130 \mu\text{mol/l}$] in men) and severe AKI to two strategies for KRT initiation. Those allocated to the accelerated strategy were to commence KRT within 12 h of meeting eligibility criteria; the standard strategy entailed deferral of KRT unless a conventional indication for KRT or persistent AKI arose. Details of the protocol, analysis, and findings have been previously reported [3, 13, 14].

Patients We included all patients from the modified intention-to-treat analysis ($n=2927$).

Endpoints The primary endpoint was 90-day all-cause mortality. Key secondary endpoints included: (1) number of days alive and free of KRT and (2) days alive and free of hospitalization, both through 90 days. Additional secondary endpoints included: (3) composite for death/KRT at 90 days; (4) KRT dependence at 90 days among survivors; and (5) rehospitalization within 90 days.

Statistical Analysis We defined a priori that the model would be a Bayesian Hierarchical model adjusted for the presence of sepsis (Yes/No), type of ICU admission (surgical vs. medical) and baseline chronic kidney disease (CKD) status, defined as premorbid estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² (Yes/No), with study site added as a random intercept [see: data creation plan (DCP) at <https://www.ualberta.ca/critical-care/research/current-research/starrtaki/documents.html>].

We considered neutral, optimistic, and pessimistic priors. The priors were defined on a log scale for the odds ratio (OR) and assumed a normal distribution. The neutral prior was defined so that 0.95 of the probability mass ranged from an odds ratio between 0.5 and 2.0; that is, it follows a normal distribution defined as $N(\text{mean}, \text{standard deviation})$ equals to $N(0, 0.355)$. The optimistic and pessimistic priors were mirrored around the effect size that the STARRT-AKI trial was

designed to detect (a 6% absolute risk reduction in 90-day all-cause mortality from 40 to 34%, representing an $OR = 0.77$ [$\log[OR] = -0.257$]). Standard deviation was set to consider a 0.15 probability of harm for the optimistic prior and 0.15 probability of benefit for the pessimistic prior; that is, the optimistic prior was centered in a possible benefit ($\log[OR] = 0.257$; $OR \sim 0.77$), while acknowledging the possibility of harm, and the pessimistic prior was centered at possible harm ($\log[OR] = -0.257$; $OR \sim 1.30$), while considering a 0.15 probability of benefit [9]. Under these assumptions, the optimistic prior was $N(-0.257, 0.249)$ and pessimistic prior was $N(0.257, 0.249)$. Priors for other predictors were set as $N(0, 1)$ for regularization. Default priors for random intercepts in *brms* R package were used [15].

We report the following metrics for the intervention (accelerated strategy) on the primary endpoint: (1) median of the posterior distribution; (2) posterior distribution 95% highest density interval (HDI); (3) probability of direction (PD; the probability that the effect size is on the side of the point estimate); (4) probability of “significance” based on a region of practical equivalence defined using traditional criteria; and (5) probability that the effect size is at least equal to or greater than what was considered as a minimal clinically important difference (MCID) in favor of the intervention, as defined by a survey of the STARRT-AKI international steering committee members (see Additional file 1); (6) probability that the effect size is at least 1.5 times higher than the one defined as MCID (which we considered as a “large” effect). The thresholds beyond which the effect was considered as “significant” were based on a difference in $\log(OR)$ that is equivalent of a standardized mean difference of 0.1 in Cohen’s d scale [equivalent to a $\log(OR)$ difference of 0.18; to convert from Cohen’s d to standardized $\log(OR)$ difference in Cohen’s d scale, multiply the $\log(OR)$ by $\pi/\sqrt{3}$], which would translate to an odds ratio between 0.83 and 1.19 [16, 17]. These parameters were used to define the region of practical equivalence (ROPE) for this analysis; these values, albeit somewhat arbitrary, are considered as reasonable for equivalence testing [16, 17]. We defined percentage inside ROPE as the proportion of the whole posterior distribution that lies within the ROPE. Convergence and stability of the Bayesian sampling were assessed using R-hat, which should be below 1.01 [13], and effective sample size (ESS), which should be greater than 1000. Models were run using R package *brms* [15] and *emmeans* [18]. All analysis was run in R version 4.2.0.

Further, we also evaluated a secondary set of priors based on observations from earlier trials for the primary outcome, including: (1) the STARRT-AKI pilot trial [19]; (2) the AKIKI and ELAIN trials (given divergent results)

[2, 4]; and (3) the individual patient data meta-analysis (IPDMA) (which included all prior trials except the main STARRT-AKI trial) [20].

Secondary endpoints (days alive and KRT-free and days alive and hospital-free) were assessed using a zero–one inflated beta regression models and reported as absolute difference in days between the accelerated and standard strategies (with 95% credible intervals [CrI] of HDI) [21, 22]. We also report the conditional probability of the difference in days alive and KRT-free and hospital-free favoring the accelerated strategy and the probability that the difference is within one day more to one day fewer interval or, secondarily, higher than the consensus MCID. Other secondary binary endpoints were assessed using a similar hierarchical logistic Bayesian model as performed with the primary endpoint. Secondary outcomes were assessed using only neutral priors ($N(0, 0.355)$ for the intervention for the binary component and $N(0, 1)$ for all other variables in the model (see ESM for details), and results are presented as median difference in proportions (with 95% HDI), as well as median OR (with 95% HDI) and the probability of benefit. We report missing values for all outcomes; a complete case analysis was used for all endpoints.

Consensus for minimal clinically important difference

We surveyed the 24 members of the international steering committee of the STARRT-AKI to generate consensus on a MCID for the primary and secondary endpoints (see Additional file 1). An absolute difference of 0.04 over the baseline event rate of 0.40 for the primary endpoint, all-cause mortality at 90 days, was considered as the MCID (which results in an odds ratio of approximately 0.84; $\log(OR) = -0.175$) (see ESM). The margin for a large effect was therefore set as $1.5 \times -0.175 \approx 0.26$, which translates to a margin of large effects set as odds ratio below 0.77 or above 1.30. A margin of 3 days was considered as equivalent for the key secondary endpoints.

Results

Patients

We studied all 2927 participants (1465 allocated to the accelerated strategy and 1462 to the standard strategy) who were included in the principal modified intention-to-treat analysis presented in the main report of the trial. Mean age was 64.2, and 68% were male. Sepsis was present in 57%, and 77% were receiving mechanical ventilation at the time of randomization. A description of patient characteristics and unadjusted endpoints is shown in Table 1.

Table 1 Baseline characteristics, features, and outcomes

Characteristic*	Accelerated, N = 1465	Standard, N = 1462
Age, mean (SD)	64 (14)	64 (13)
Sex, n (%)		
Female	470 (32)	467 (32)
Male	995 (68)	995 (68)
Sepsis, n (%)	855 (58)	834 (57)
Surgical admission, n (%)	492 (34)	473 (32)
Mechanical ventilation, n (%)	1103 (75)	1148 (79)
Creatinine, mean (SD)	121 (92)	118 (87)
Chronic kidney disease, n (%)	658 (45)	626 (43)
SOFA score, median (IQR)	12 (9–14)	12 (9–14)
SAPS II score, median (IQR)	57 (45–71)	59 (47–73)
Received KRT, n (%)	1418 (97)	903 (62)
Time until KRT, hours, median (IQR)	4 (3–7)	29 (17–68)
Did not receive KRT	48	559
Outcomes		
90-day mortality n (%)	643 (44)	639 (44)
KRT dependency at 90 days, n (%)	85 (10)	49 (6)
KRT dependency or death at 90 days, n (%)	728 (50)	688 (47)
Death in hospital, n (%)	643 (44)	639 (44)
Rehospitalization at 90 days, n (%)		
No	653 (45)	685 (47)
Yes	166 (11)	138 (9)
Days alive and hospital-free at 90 days, median (IQR)	10 (0, 65)	9 (0, 64)
Days alive and KRT-free at 90 days, median (IQR)	50 (0, 87)	64 (0, 90)

*Missing values not shown in table

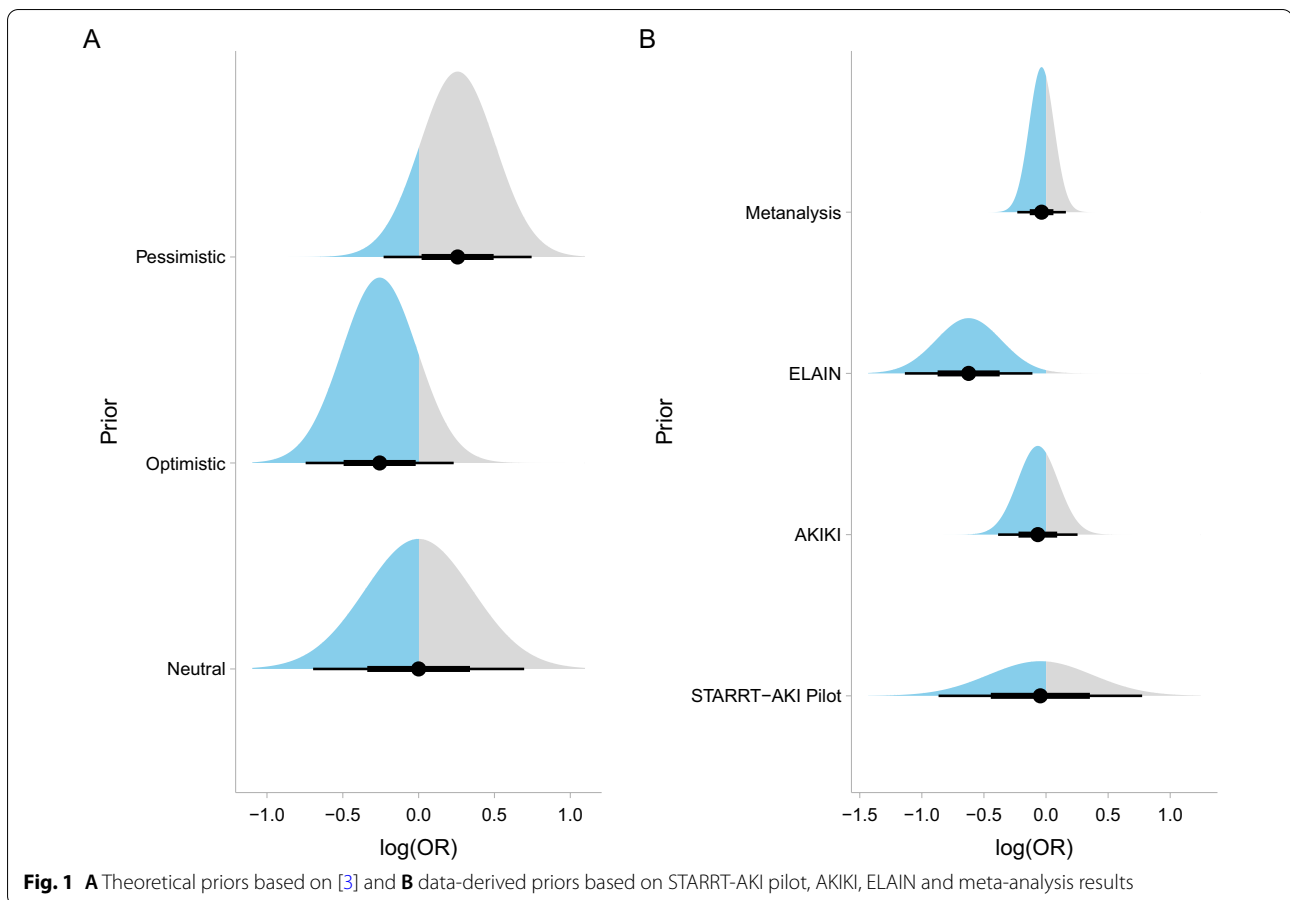
Primary endpoint: all-cause mortality at 90 days

The effect of the intervention on the primary endpoint was minimal, with only minor changes with the use of different priors. The priors used for the primary analysis are graphically shown in Fig. 1, and results for the marginal effects on both absolute and relative (OR) scales are shown in Fig. 2A, B, respectively. The posterior probabilities of effect are shown in Table 2. The results of the full model for the primary outcome using the main sets of priors are shown in Additional file 1: Table S1. There was a high probability that the effect size of the intervention was contained in the region of equivalence defined and a very low (close to zero) probability that the effect of the intervention was large. There was a negligible probability that the intervention was associated with a greater than 0.04 absolute reduction in the primary outcome (consensus MCID). In all scenarios, estimates for the absolute difference were neutral, being 0.13% (95% CrI – 3.30 to 3.40%) for the neutral prior, –0.39% (95% CrI – 3.46 to 3.00%) for the optimistic prior and 0.64% (95% CrI – 2.53 to 3.88%) for the pessimistic prior, respectively.

In the results for the data-derived priors (alternative priors), no scenario provided a posterior probability of benefit above 0.90, and both large effect sizes and effect sizes based on consensus MCID (assessed as both a low OR or a decrease in absolute probability) were very unlikely (Table 2).

Secondary endpoint: days alive and KRT-free

The distribution of days alive and KRT-free according to allocated intervention is shown in Additional file 1: Fig. S1, and results for the difference of expected predictions among groups are shown in Fig. 3A. Information was missing for 27 patients (all from the accelerated-strategy group). Patients in the accelerated strategy had fewer days alive and free of KRT, with a median absolute difference of –3.55 days fewer (95% CrI – 6.38 to –0.48 days) (Fig. 3A). The probability that the accelerated strategy was associated with more days alive and KRT-free was 0.008, the probability that this difference was within a 1 day



fewer to 1 day more range was 0.047, and the probability that this difference was within 3 days fewer to 3 days more range (consensus MCID) was 0.363. The probability that the accelerated strategy was associated with at least 3 more days alive and KRT-free was virtually zero.

Days alive and hospital-free

The distribution of days alive and free of hospitalization according to allocated intervention is shown in Additional file 1: Fig. S2, and results for the difference of expected predictions among groups are shown in Fig. 3B. Information was missing for 1 patient in the accelerated-strategy group. The accelerated strategy had a median absolute difference of 0.48 days more alive and hospital-free (95% CrI -1.87; 2.72). The probability that the accelerated strategy was associated with more days alive and hospital-free was 0.657, the probability that this difference was within a 1 day more to 1 day fewer range was 0.566, and the probability that the difference was within a 3 day more to 3 day fewer range (consensus MCID) was 0.983. The probability that the accelerated strategy was associated with at least 3 more days alive and hospital-free was only 0.015.

Additional secondary endpoints

The composite endpoint of KRT dependency at 90 days or death was missing in 16 patients (8 in accelerated and 8 in the standard-strategy group). A total of 728 (49.7%) had the composite outcome in the accelerated strategy, and 688 (47.1%) had the composite outcome in standard strategy, respectively (Table 1). The adjusted absolute difference was 2.38% (95% HDI -1.13 to 5.77%). The median OR was 1.10 (95% HDI 0.95–1.26; Fig. 4A). The posterior probability of benefit with the accelerated strategy was 0.086.

A total of 1,629 patients survived hospital discharge and had KRT data available (814 in the accelerated and 815 in the standard strategy). KRT dependency at 90 days occurred in 85 (10.44%) and 49 (6.01%) patients in the accelerated and standard strategies, respectively, with a median adjusted difference 3.82% (95% HDI 1.40–6.42%) and the median OR was 1.59 (95% HDI 1.15–2.13; Fig. 4B). The posterior probability of benefit with the accelerated strategy was below 0.001.

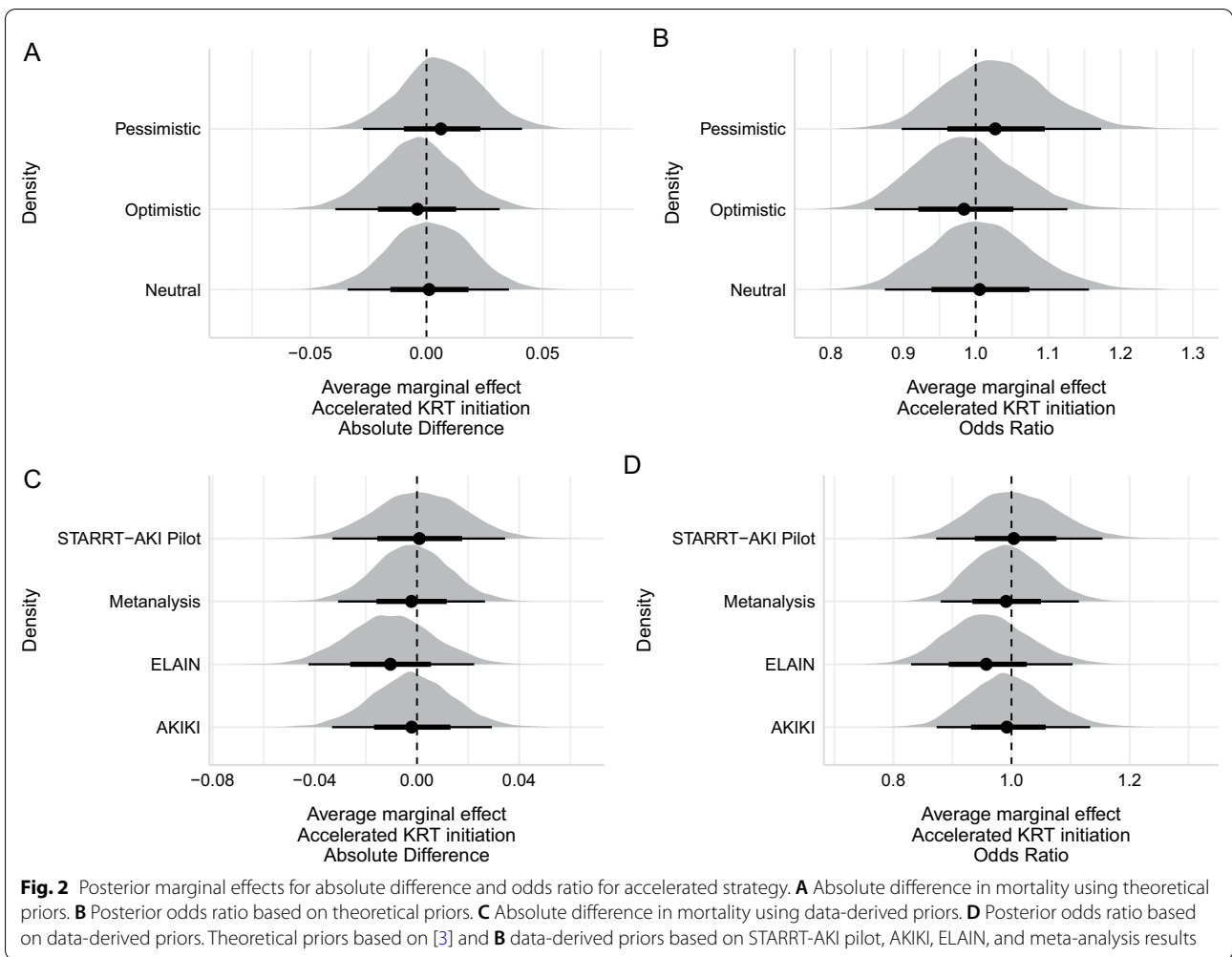


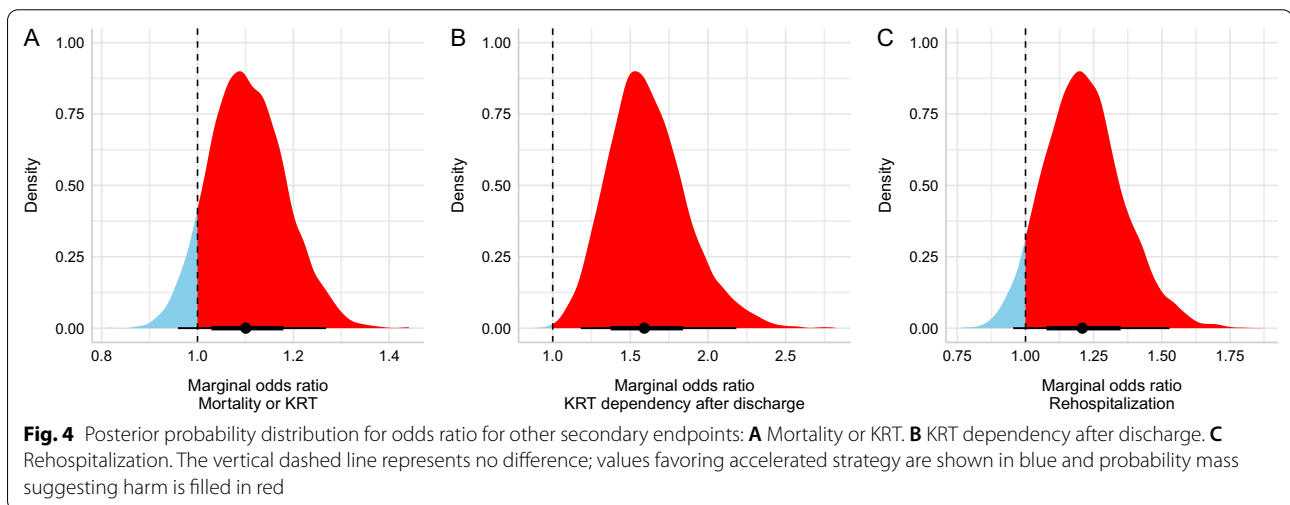
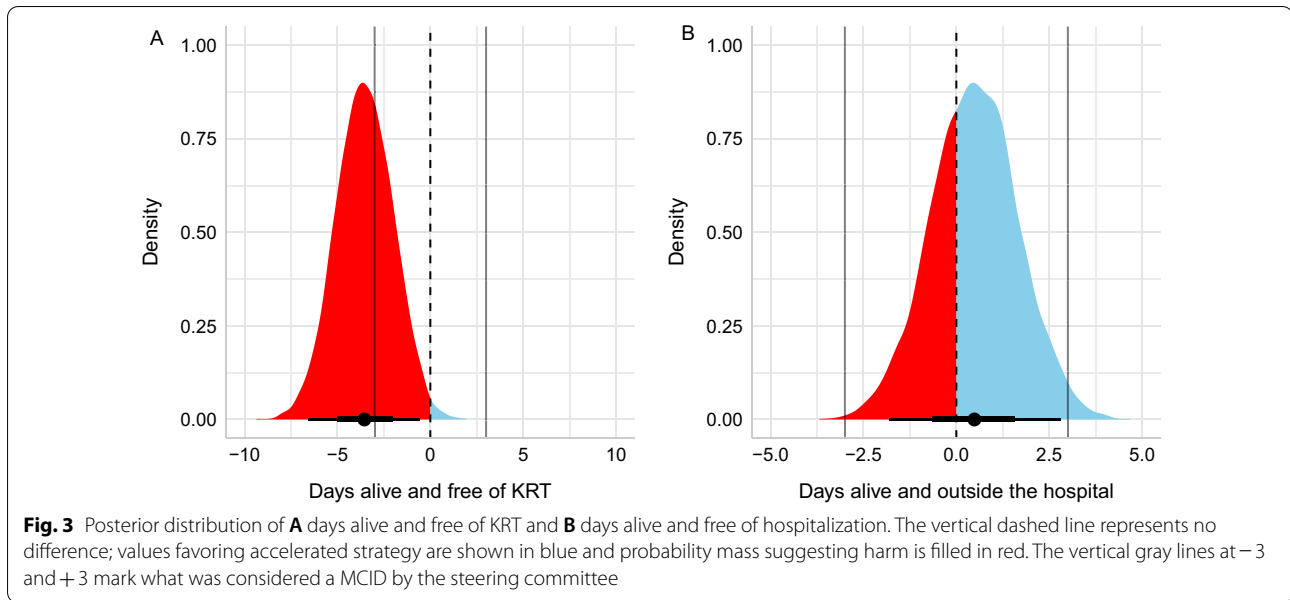
Table 2 Results for the primary endpoint according to different priors

Prior	Median	HDI 95%	<i>P</i> (Benefit)*	%ROPE**	<i>P</i> (effect not large) [‡]	<i>P</i> (OR < 0.84) [†]	<i>P</i> (diff < -0.04) [¶]
<i>Theoretical priors</i>							
Neutral	1.01	0.87–1.15	0.47	0.99	1.00	0.00	0.01
Optimistic	0.98	0.86–1.12	0.59	0.99	1.00	0.00	0.02
Pessimistic	1.03	0.90–1.18	0.35	0.99	1.00	0.00	0.00
<i>Data driven priors</i>							
AKIKI	0.99	0.87–1.13	0.54	0.99	1.00	0.00	0.01
ELAIN	0.96	0.83–1.10	0.73	0.97	1.00	0.00	0.04
Meta-analysis	0.99	0.88–1.12	0.56	0.99	1.00	0.00	0.00
STARRT-AKI Pilot	1.00	0.87–1.15	0.48	0.98	1.00	0.00	0.01

*Probability OR < 1.0. **Probability effect size (OR) is within 0.83–1.19 (equivalence margin). †Probability effect size is outside a large margin effect of OR between 0.77 and 1.30. ‡Probability OR is below 0.84 (which results in a 4% reduction in primary outcome). ¶Probability the difference is outcome is greater than 4% favoring accelerated strategy given the data and prior

A total of 1642 patients survived to hospital discharge. Rehospitalization occurred in 166 (20.27%) patients in the accelerated strategy and 138 (16.77%)

patients in the standard strategy, respectively. The adjusted difference was 2.87% (95% HDI -0.50 to 6.57%), and the median OR was 1.21 (95% HDI



0.93–1.49, Fig. 4C). The posterior probability of benefit with the accelerated strategy was 0.056.

Discussion

In this post hoc Bayesian reanalysis of STARRT-AKI, the largest international randomized trial of acute KRT, we found that the probability that an accelerated strategy was associated with a clinically important or large treatment effect on 90-day all-cause mortality is very low. These findings were consistent across a spectrum of priors used to inform our Bayesian models, including the results from prior trials with conflicting results [1, 2, 4]. In addition, we found high probabilities that the accelerated strategy resulted in fewer KRT-free days, as well as a higher risk of

KRT dependence and rehospitalization at 90 days (all probabilities exceeding 0.90) compared with the standard strategy. These findings greatly extend the main frequentist analysis of the STARRT-AKI trial previously reported, by drawing emphasis on the exceedingly low likelihood of any meaningful benefit with a strategy of accelerated KRT initiation [3]. While trials have utilized varying definitions of “accelerated” or “early” and “standard” or “delayed” to define the timing of KRT initiation, the findings of this analysis should strongly reinforce the adoption of a “watch and wait” strategy, where clinician decision-making on when to start KRT for critically ill patients with AKI should be prompted by development of conventional indications, medically refractory complications and/or persistent AKI [3, 21].

The use of Bayesian reanalysis provides a unique opportunity to reappraise, augment, and expand the main results of large, randomized trials using an alternative framework [10]. A Bayesian approach, integrating the concepts of probabilities of benefit or harm for a given intervention, may better mimic how clinicians integrate information to make clinical decisions at the bedside. This may have greater relevance for resource-intensive interventions with known risk profiles, such as KRT [22]. In this reanalysis, we “stressed” the STARRT-AKI trial data with seven different priors for the primary endpoint of 90-day all-cause mortality (with only minor deviations in results). We further provided probabilistic interpretations of the primary and secondary outcomes based not only on thresholds for treatment effect sizes [16, 17], but also by defining a minimal clinically important difference (MCID) from a consensus of the STARRT-AKI trial’s lead investigators.

Establishing a MCID can be challenging. This can often be based on cost-effectiveness analyses or quality-adjusted life years [23] and is increasingly being adopted across disciplines and in clinical trial design [24]. Despite this, there is surprisingly little guidance on how to best define MCID in critical care [25, 26]. We used a very simple consensus analysis based on the expert opinion of the international steering committee of the STARRT-AKI trial [3]. Though imperfect, this approach enabled a global perspective from clinicians who are deeply involved in critical care nephrology. First, there was consensus that 4% absolute difference in the primary endpoint of all-cause mortality at 90 days could be considered as a MCID. In the main STARRT-AKI analysis, we reported a relative risk of 1.00 (95% CI 0.93–1.09) [3], that is, an absolute difference of 0, with the data being compatible under the null hypothesis to values in the range of a 7% reduction or 9% increase in 90-day all-cause mortality. Therefore, the main analysis was not able to theoretically rule out what could be considered a MCID, as defined by consensus for this analysis, since the 4% absolute reduction was within range of the reported treatment effect size under the frequentist paradigm. The findings of this Bayesian reanalysis can virtually eliminate the possibility that a 4% absolute reduction in the primary endpoint was compatible with the trial data, regardless of the variation in priors used to inform the analysis. Likewise, we were able to conclude with high probability that the accelerated strategy conferred greater KRT dependence, rehospitalization, and fewer KRT-free days when compared to a standard strategy for KRT initiation.

There are limitations to our analysis that warrant consideration. First, this secondary analysis was post hoc; however, we developed an a priori analytic plan prior to data analysis. Second, we recognize that priors used in Bayesian

analysis are subjective. To address this, we used a range of priors, including those derived from prior trial data and consensus. Third, we did not impute for missing data. Fourth, we did not adjust for multiplicity of testing, though the concern for type I error may be reduced with Bayesian analysis compared with a frequentist analysis, and our findings were coherent with the main STARRT-AKI trial [3, 11]. Fifth, we used margins for equivalence and for defining large effect sizes that may be questionable; however, we also present results based on consensus definition of MCID, which corroborates with consistent interpretation.

Conclusions

This Bayesian reanalysis of the STARRT-AKI trial showed that there is a very low probability that an accelerated KRT strategy will lead to a clinically important improvement in 90-day all-cause mortality. In addition, patients who were allocated to the accelerated strategy probably had fewer KRT-free days, and a higher probability of 90-day KRT dependence and rehospitalization. Collectively, these findings do not support adoption of an early or accelerated strategy for KRT initiation.

Abbreviations

AKI: Acute kidney injury; CrI: Credible interval; GFR: Glomerular filtration rate; HDI: High-density interval; ICU: Intensive care unit; IPDMA: Individual patient data meta-analysis; KRT: Kidney-replacement therapy; MCID: Minimal clinically important difference; ROPE: Range of practical equivalence.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13054-022-04120-y>.

Additional file 1. Analysis overview for the key secondary outcomes. **eTable 1.** Full model report according to theoretical priors. **eFigure 1.** Distribution of days alive and KRT-free according to allocated strategy. **eFigure 2.** Distribution of days alive and free of hospitalization according to allocated strategy. Consensus definitions for equivalence, minimal clinically important difference (MCID), and large effects. STARRT-AKI Investigators.

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Author contributions

SMB, FGZ, and RW conceived and designed the study. SMB and RW acquired the data. FGZ, BRC, and SMB performed analysis; all authors interpreted data; FGZ and SMB drafted the manuscript; all authors provided substantial revisions; all authors have reviewed and approved the submitted manuscript; and all authors have agreed both to be personally accountable for the author’s own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. All authors read and approved the final manuscript.

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Availability of data and materials

The STARRT-AKI has a data sharing policy available at: <https://www.ualberta.ca/critical-care/research/current-research/starttaki/documents.html>

Declarations

Ethics approval and consent to participate

The STARRT-AKI trial was approved by the health research ethics boards at the University of Alberta (File # Pro00060023) and Unity Health Toronto (CTO Project ID: 0761) and the institutional review boards at each participating site. Depending on local standards and legislation, informed consent was obtained from patients and substitute decision-makers or through waived consent.

Consent for publication

Not applicable.

Competing interests

FGZ has received Grants for investigator initiated clinical trials from Bactiguard (Sweden) and Ionis Pharmaceuticals (USA), unrelated to this work. FGZ has performed statistical consulting for Bactiguard (Sweden). FGZ does not own stocks, neither has been reimbursed for travels or has received speaking fees. MO has received speaker fees and research funding from Baxter and Fresenius Medical Care. SMB has received speaker and Scientific Advisory fees and unrestricted research funding from Baxter and Scientific Advisor fees from Novartis and BioPorto. RW has received unrestricted research funding from Baxter.

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