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MAJOR ARTICLE

Longer-term Mortality and Kidney Outcomes of Participants in the Combination Antibiotics for Methicillin-Resistant *Staphylococcus aureus* (CAMERA2) Trial: A Post Hoc Analysis

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Background. The Combination Antibiotic Therapy for Methicillin-Resistant *Staphylococcus aureus* (CAMERA2) trial ceased recruitment in July 2018, noting that a higher proportion of patients in the intervention arm (combination therapy) developed acute kidney injury (AKI) compared to the standard therapy (monotherapy) arm. We analyzed the long-term outcomes of participants in CAMERA2 to understand the impact of combination antibiotic therapy and AKI.

Methods. Trial sites obtained additional follow-up data. The primary outcome was all-cause mortality, censored at death or the date of last known follow-up. Secondary outcomes included kidney failure or a reduction in kidney function (a 40% reduction in estimated glomerular filtration rate to <60 mL/minute/1.73 m^2). To determine independent predictors of mortality in this cohort, adjusted hazard ratios were calculated using a Cox proportional hazards regression model.

Results. This post hoc analysis included extended follow-up data for 260 patients. Overall, 123 of 260 (47%) of participants died, with a median population survival estimate of 3.4 years (235 deaths per 1000 person-years). Fifty-five patients died within 90 days

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after CAMERA2 trial randomization; another 68 deaths occurred after day 90. Using univariable Cox proportional hazards regression, mortality was not associated with either the assigned treatment arm in CAMERA2 (hazard ratio [HR], 0.84 [95% confidence interval [CI], .59–1.19]; $P = .33$) or experiencing an AKI (HR at 1 year, 1.04 [95% CI, .64–1.68]; $P = .88$).

Conclusions. In this cohort of patients hospitalized with methicillin-resistant *S aureus* bacteremia, we found no association between either treatment arm of the CAMERA2 trial or AKI (using CAMERA2 trial definition) and longer-term mortality.

Keywords. acute kidney injury; nephrotoxicity; *Staphylococcus aureus* bacteremia.

Acute kidney injury (AKI) is a clinical syndrome characterized by a sudden reduction in glomerular filtration rate (GFR) diagnosed by an increase in serum creatinine concentration and a reduction in urine output [1]. Following AKI, patients have an increased risk of death, progression to chronic kidney disease, myocardial infarction, hypertension, and sepsis [2–4]. Studies of AKI outcomes have included heterogenous patient groups and, consequently, prognosis following AKI in specific clinical scenarios is not well categorized.

The Combination Antibiotic Therapy for Methicillin-Resistant *Staphylococcus aureus* (CAMERA2) trial was a multicenter randomized controlled trial in adults with methicillin-resistant *S aureus* (MRSA) bloodstream infection [5]. It aimed to determine whether 7 days of intravenous β-lactam therapy in combination with standard MRSA therapy (vancomycin or daptomycin) led to better 90-day complication-free survival compared to standard MRSA therapy (ie, monotherapy). The data safety and monitoring board recommended ceasing recruitment in July 2018 due to a higher rate of patients in the combination treatment arm developing AKI (23% vs 6%; $P < .001$) and no difference in the primary outcome (a composite of 90-day mortality, microbiological persistence, relapse, or treatment failure).

Here, we provide longer-term follow-up of CAMERA2 participants, specifically focusing on the effect of treatment arm and AKI on mortality, kidney failure (ie, maintenance dialysis or transplant), or reduction in kidney function (a 40% reduction in estimated GFR [eGFR] to a final eGFR <60 mL/minute/1.73 m^2).

METHODS

Study Design and Population

The CAMERA2 trial (ClinicalTrials.gov identifier NCT02365493) was a prospective, multicenter, open-label, randomized trial in hospitalized adult patients with MRSA bacteremia between August 2015 and July 2018. Full trial methodology and patient recruitment have been described previously [5, 6]. Data collection for this follow-up analysis was undertaken from June to October 2021.

For this post hoc analysis, all patients enrolled into the CAMERA2 trial were considered for inclusion. Patients were excluded from this analysis if they were receiving chronic hemodialysis or peritoneal dialysis before enrollment. Due to workload related to the coronavirus disease 2019 pandemic, some sites were unable to collect data and we did not have ethical approval to include patients from New Zealand. Ethical approval was obtained for all other sites contributing data as an amendment to the CAMERA2 trial at relevant Human Research Advisory Committees. Relevant patient demographic data and clinical covariates were obtained from the CAMERA2 database. Baseline creatinine was defined as the highest creatinine measurement in the 24 hours preceding randomization. AKI diagnosis in this analysis used the CAMERA2 criteria of modified risk, injury, failure, loss, and end-stage kidney (mRIFLE) criteria (a 1.5-fold increase in the serum creatinine or GFR decrease by 25% at any time within the first 7 days, or new need for renal replacement therapy at any time from day 1 to day 90).

Data Collection

Trial sites entered follow-up data into a purpose-built Research Electronic Data Capture (REDCap) database. Follow-up data were derived from health records or pathology results at each institution and included vital status, date of death, progression to kidney failure, the date of transplant or initiation of dialysis, and serum creatinine concentration in the following periods after randomization: 3–6 months, 6–9 months, 9–12 months, 1–2 years, and the most recent creatinine available after 2 years. If >1 creatinine was available in a time period, the lowest creatinine in each time period in the first year (3–6 months, 6–9 months, and 9–12 months follow-up) was used, and the latest creatinine in each time period in the following years.

The date of last known follow-up was recorded for each patient. Only existing clinical and pathology data accessible by the participating health service were used; no additional information or samples for testing were required.

Outcome Measures

The primary outcome was all-cause mortality, censored at death or the date of last known follow-up. Secondary outcomes included progression to kidney failure or a reduction in kidney function. Kidney failure was defined as kidney transplantation or initiation of maintenance dialysis for at least 4 weeks as per international consensus definitions [7]. A reduction in kidney function was defined as a 40% reduction in eGFR from CAMERA2 enrollment, or trial day 2 if an enrollment creatinine was not available, to the eGFR at last known follow-up and a final eGFR <60 mL/minute/1.73 m^2. This GFR-based outcome is predictive of progression to kidney failure in observational studies and is based on the published international

consensus definitions of clinical trial outcomes for kidney failure [7]. The international consensus definitions recommend confirming the GFR reduction with a second creatinine at least 4 weeks later. With our pragmatic approach, sites were asked to only provide 1 creatinine result for each time period. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, without the correction factor for African American patients. In Indigenous Australians, the CKD-EPI formula without the African American correction factor has been shown to be accurate [8].

Statistical Analysis

Incidence rates were calculated overall and by time period since enrollment in CAMERA2 and are presented by treatment arm as events per 1000 person-years. Time zero was the day of randomization, failure was death from any cause, and follow-up was censored at date of death or the last known date alive.

All patients were included in the survival analysis of mortality (Figure 1). For longer-term kidney outcomes, patients who died during the CAMERA2 follow-up period (n = 55) or started chronic renal replacement therapy (RRT) within 90 days of randomization were excluded (n = 1). For the outcome of kidney failure, those confirmed to be alive beyond day 90 post-CAMERA2 randomization but with no record of receiving chronic dialysis were assumed not to have progressed to dialysis (n = 12), and patients with no follow-up data beyond day 90 postrandomization were excluded (n = 16). For patients known to be alive beyond day 90 after trial enrollment without any further creatinine concentrations available, reduction in kidney function was coded as missing data and excluded from analysis for this outcome (n = 28).

Kaplan-Meier survival curves for the primary outcome were produced for each categorical variable considered, including sex, country, treatment arm, AKI in CAMERA2, persistent bacteremia, and RRT in CAMERA2. We assessed the association between the primary outcome and covariates using Cox proportional hazard regression models in univariable and multivariable analysis. Kaplan-Meier curves and likelihood ratio tests for univariable models using a time-varying covariate were used to test the assumption of proportional hazards for the primary outcome. AKI was included in the Cox proportional hazard regression model as a time-varying covariate. Where the likelihood ratio test indicated that the proportional hazard assumption was violated and the distribution of the variable was highly skewed, for continuous variables, categorical versions of these variables were used (based on clinical knowledge). For categorical variables where the likelihood ratio test indicated that the proportional hazard assumption was violated, these were included as time-varying covariates. We undertook a landmark sensitivity analysis using follow-up time starting 7 days after CAMERA2 enrollment and only including those who survived to CAMERA2 trial day 7.

All variables, including time-varying covariates, with a P value < .10 from univariate analysis were included in the multivariable model, with a planned backwards stepwise variable selection process to determine the independent predictors of mortality. Decades of age were used to account for different age-related mortality risk.

Statistical analyses were conducted using Stata software version 15.1 (StataCorp LLC, College Station, Texas).

RESULTS

This follow-up analysis included 260 of the 356 patients from the CAMERA2 trial (Figure 1). Follow-up duration per patient ranged from 2 days to 5.7 years, providing 523 person-years of follow-up data. Characteristics of this follow-up cohort are provided in Table 1.

Overall, 123 patients (47%) died between randomization and last follow-up (n = 260). This represents 235 deaths per 1000 person-years (95% confidence interval [CI], 197–281 person-years) (Table 2). Fifty-five patients (21% of total cohort) died within the 90 days after randomization to CAMERA2, with another 68 deaths (26%) occurring after 90-day follow-up. Overall population median survival by Kaplan-Meier estimate was 3.4 years.

Age, sex, Pitt bacteremia score, Charlson comorbidity index score, and Sequential Organ Failure Assessment (SOFA) score were similar between the 352 randomized patients from the CAMERA2 cohort compared to the 260 included in this analysis: median age, 64 years (interquartile range [IQR], 49–76.5 years) versus 64.5 years (IQR, 49–79 years); proportion male, 66% versus 65%; Pitt bacteremia score, 2 (IQR, 2–3) versus 2 (IQR, 2–3); Charlson comorbidity index score, 5 (IQR, 2–7) versus 5 (IQR, 2–7); and SOFA score, 1 (IQR, 0–3) versus 2 (IQR, 0–4), respectively.

Mortality was 65 of 129 (50%) in patients randomly assigned to the combination therapy arm compared to 58 of 131 (44%) patients in the standard therapy arm (follow-up times provided in Table 2). Treatment arm was not associated with mortality (hazard ratio [HR], 0.84 [95% CI, .59–1.19]; $P = .33$). AKI in the CAMERA2 trial occurred in 49 patients in this follow-up cohort. AKI was not associated with mortality (at 1 year: HR, 1.03 [95% CI, .64–1.68]; $P = .88$). Median follow-up for those with AKI was 1.4 years (IQR, 45 days to 3.5 years), and for those without AKI was 1.65 years (IQR, 78 days to 3.6 years). Additionally, when only including patients who survived to day 7 (n = 249) and using follow-up time starting 7 days after CAMERA2 enrollment, AKI was not associated with mortality (HR, 1.12 [95% CI, .68–1.83]; $P = .66$).

Of the patients who required RRT during the first 90 days after CAMERA2 randomization (n = 8), RRT was ceased in 3 (37%) by day 90 and not restarted, 4 died before day 90 (50%), and 1 patient had maintenance haemodialysis continued beyond day 90 (12.5%).

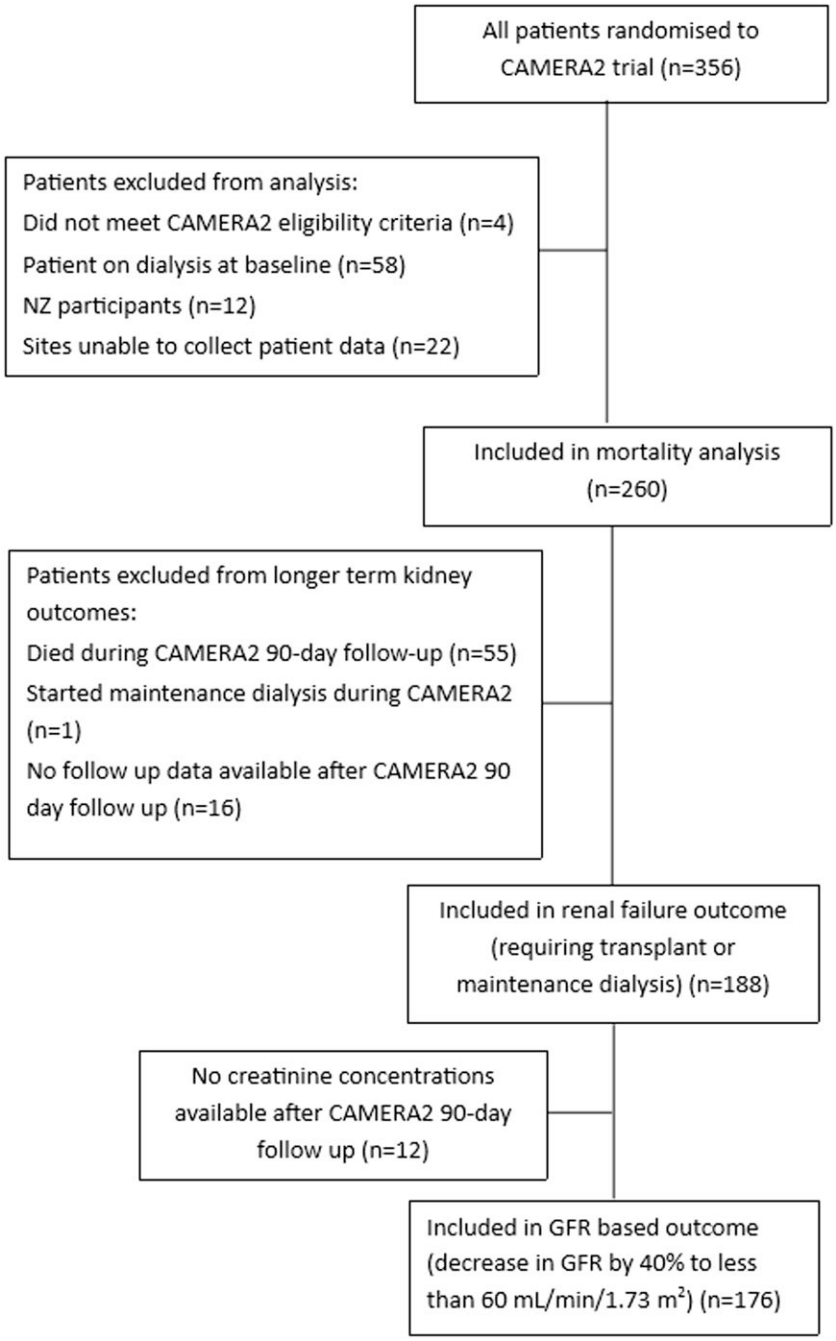

Figure 1. Study flowchart. Abbreviations: CAMERA2, Combination Antibiotic Therapy for Methicillin-Resistant *Staphylococcus aureus*; GFR, glomerular filtration rate; NZ, New Zealand.

After the CAMERA2 90-day follow-up period, no patient underwent kidney transplantation and 5 patients newly developed kidney failure requiring initiation of maintenance dialysis. All 5 patients did not experience AKI prior to day 90. Progression to kidney failure occurred in 2 of 91 (2.2%) participants from the combination therapy arm and 3 of 97 (3.1%) from the standard therapy arm. Median follow-up was 3.6 years (IQR, 3.5–3.6 years) in those who progressed to kidney failure, and 3 years (IQR, 1.4–4.1 years) for those who did not.

Reduction in kidney function (decrease in eGFR of ≥40% and a final eGFR <60 mL/minute/1.73 m^2), was seen in 19 of 85 (22%) patients from the combination therapy arm and 16 of 91 (18%) patients in the standard therapy arm. Reduction in kidney function beyond 90 days after CAMERA2 randomization occurred in 7 of 27 (26%) patients with AKI and 28 of

Table 1. Baseline Characteristics of 260 Participants

Characteristic	Combination Therapy (n = 129)	Standard Therapy (n = 131)
Age at trial enrollment, years, median (IQR)	64 (48–76)	65 (53–81)
Female sex	39 (30)	52 (40)
Country		
Australia	93 (72)	94 (72)
Israel	19 (15)	19 (14)
Singapore	17 (13)	18 (14)
Charlson comorbidity index score, median (IQR)	5 (2–7)	5 (2–8)
Pitt bacteremia score, median (IQR)	2 (2–3)	2 (2–3)
SOFA score, median (IQR)	2 (0–3)	1 (0–3)
Recognized infection foci at time of index blood culture		
Skin and soft tissue	35 (27)	44 (34)
Primary bloodstream	28 (22)	25 (19)
Native osteoarticular	23 (18)	19 (15)
Intravenous line related	11 (9)	5 (4)
Pleuropulmonary	11 (9)	9 (7)
Device related	6 (5)	8 (6)
Infective endocarditis	4 (3)	6 (5)
CNS related	1 (1)	3 (2)
Other	10 (8)	12 (9)
Baseline creatinine, μmol/L, median (IQR) (n = 248)	86.5 (66–145)	86 (66–150)
Experienced AKI[a]	37 (29)	12 (9)
Follow-up time from trial enrollment, d, median (IQR)	505 (77–1314)	612 (68–1380)
Time at risk, person-years	249.59	273.33
Population survival estimate, y, median (IQR)	2.7 (0.3, NA)	4.1 (0.4, NA)
Died	65 (50)	58 (44)
Progressed to RRT >90 d after CAMERA2 randomization (n = 188)[b]	2 (2)	3 (2)
Reduction in kidney function beyond 90 d[c,d] (n = 176)	19 (22)	16 (18)
Change in eGFR (mL/min/1.73 m^2) from CAMERA2 enrollment to last follow-up, median, (IQR) (n = 176)[d]	−7 (+8.1 to −22.5)	−7 (+6.2 to −21.4)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: AKI, acute kidney injury; CAMERA2, Combination Antibiotic Therapy for Methicillin-Resistant *Staphylococcus aureus*; CNS, central nervous system; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NA, not applicable; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment.

[a]AKI defined in CAMERA2 trial using modified risk, injury, failure, loss, and end-stage kidney (mRIFLE) criteria (a 1.5-fold increase in the serum creatinine or GFR decrease by 25% at any time within the first 7 days, or new need for renal replacement therapy at any time from day 1 to 90, per CAMERA2 study protocol).

[b]Kidney failure outcome. RRT was defined as maintenance dialysis for >4 weeks or kidney transplant.

[c]Reduction in kidney function eGFR was defined as a 40% reduction in eGFR and a final eGFR <60 mL/min/1.73 m^2.

[d]Used CAMERA2 baseline creatinine concentration (or trial day 2 if creatinine unavailable at baseline).

149 (19%) without AKI. Median follow-up for those with a reduction in kidney function was 2.9 years (IQR, 0.8–3.7 years), and 3.2 years (IQR, 1.4–4.1 years) for those without.

Table 2. Incident Death Rates During Follow-up

Follow-up Period[a]	Treatment Arm	No. of Deaths	Person-time, y	Incidence Rate per 1000 PY (95% CI)
0–90 d	All	55	53.59	1026 (788–1337)
	Combination	29	26.37	1100 (764–1582)
	Standard	26	27.22	955 (650–1403)
90–180 d	All	15	44.40	338 (204–560)
	Combination	8	21.32	375 (188–750)
	Standard	7	23.08	303 (145–363)
180–365 d	All	17	78.64	216 (134–348)
	Combination	12	37.11	323 (184–569)
	Standard	5	41.53	120 (50–289)
1–3 y	All	26	240.08	108 (74–159)
	Combination	13	115.73	112 (65–193)
	Standard	13	124.35	105 (61–180)
>3 y	All	10	106.21	94 (50–175)
	Combination	3	49.06	61 (20–190)
	Standard	7	57.15	123 (58–257)
Overall	All	123	522.92	235 (197–281)
	Combination	65	249.59	260 (204–332)
	Standard	58	273.33	212 (164–274)

Abbreviations: CI, confidence interval; person-years.

[a]Time 0 is enrollment in the Combination Antibiotic Therapy for Methicillin-Resistant *Staphylococcus aureus* (CAMERA2) trial.

The Kaplan-Meier survival curves for the primary outcome of mortality for all patients, and stratified by treatment arm or experiencing an AKI during CAMERA2, are provided in Figure 2. Kaplan-Meier survival curves with CIs and censoring and likelihood ratio tests comparing univariable Cox regression models to assess whether covariates are time dependent are provided in the Supplementary Materials.

Clinical covariates associated with mortality from univariate analysis included age, country of enrollment, Charlson comorbidity index score, SOFA score, Pitt bacteremia score, and baseline creatinine concentration (Table 3). Median age of enrollment differed across countries (median age of enrollment: 62 years in Australia, 75.5 years in Israel, 68 years in Singapore), as did median Charlson comorbidity index score (4 in Australia, 5.5 in Israel, 7 in Singapore).

Age, country of enrollment, Charlson comorbidity index score, SOFA score, Pitt bacteremia score, and baseline creatinine concentration were found to be independent predictors of mortality in the Cox regression model (Table 3).

DISCUSSION

In this cohort of patients with MRSA bacteremia, longer-term mortality was high, with 47% of patients dying over the follow-up period and a median population survival estimate of 3.4 years. Despite previous data linking AKI to poorer long-term outcomes and AKI predominantly occurring in the combination therapy arm in CAMERA2, in this analysis neither

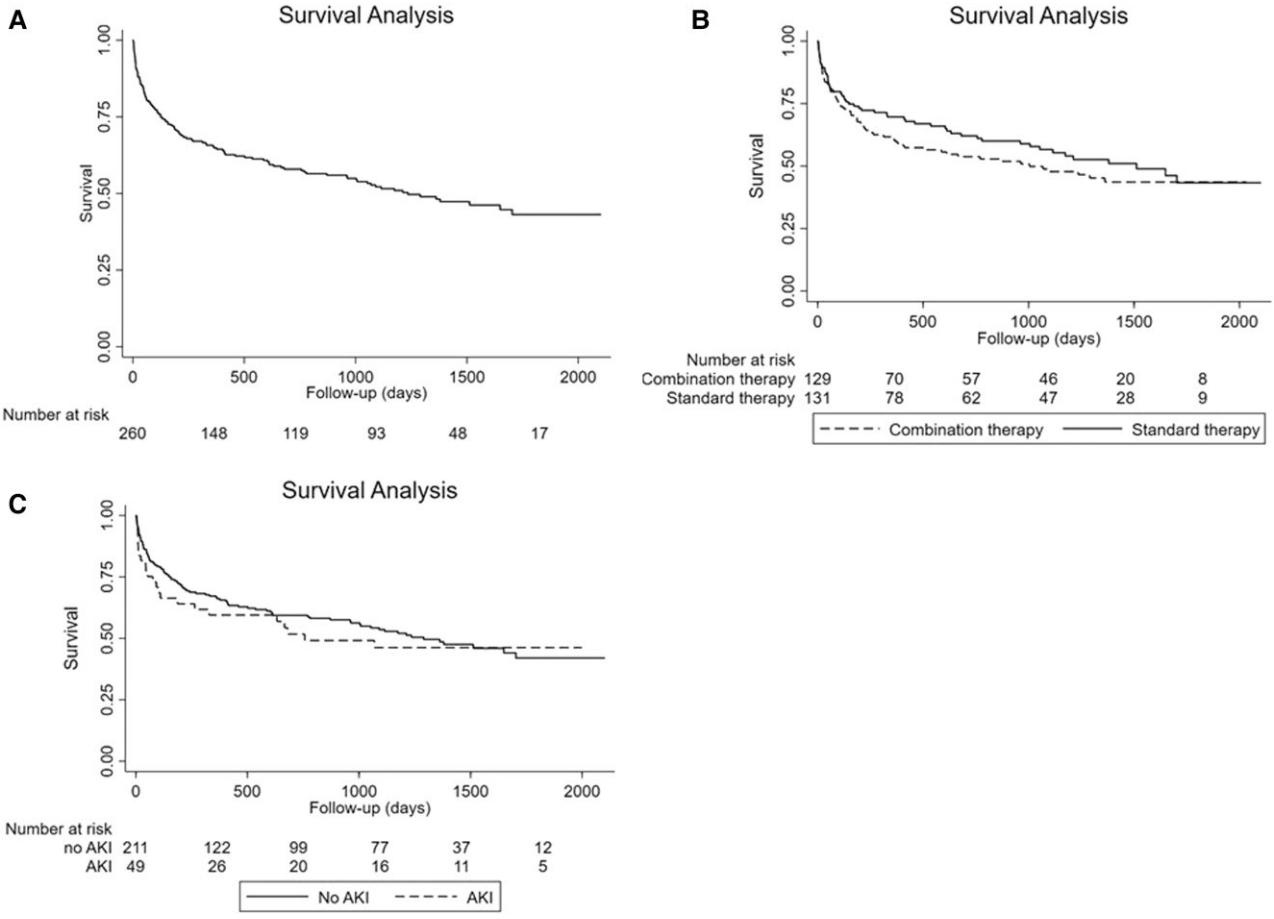

Figure 2. Kaplan-Meier survival curves for the primary outcome of mortality overall (*A*), by Combination Antibiotic Therapy for Methicillin-Resistant *Staphylococcus aureus* (CAMERA2) treatment arm (*B*), and by acute kidney injury (AKI) (*C*) in the CAMERA2 trial.

randomization to the combination arm, nor experiencing an AKI, was statistically associated with death. Presenting characteristics of patients across countries likely influenced mortality rates.

In the majority of studies relating to *S aureus* bacteremia (SAB), follow-up duration is limited; usual follow-up durations are 30 or 90 days after the index blood culture. Our analysis adds to the limited body of literature reporting longer-term outcomes and showing high mortality rates after SAB. For patients with MRSA bacteremia, mortality has been reported as 46.2% at 1 year, 36.4% at 5 years, and 75% at 14 years [9–11]. For patients with any SAB, mortality at 1 year ranges from 30% to 62%, while longer-term mortality has been reported at 3 years (45.2%), 4 years (69%), and 5 years (35%–72%) [12–24]. Methicillin-susceptible *S aureus* is associated with lower mortality than MRSA, and combined *S aureus* cohorts may dilute the mortality for MRSA [25]. The increased mortality from MRSA bacteremia may be due to factors unrelated to the bacteria itself, such as patient comorbidities, delays in administration of effective antibiotics, and severity of infection [9, 11, 26].

In our analysis, the highest mortality rate was seen in the 90 days following bacteremia, with a decrease over the remainder of the follow-up period, as seen in other population cohort studies [15, 17]. Our analysis may underestimate true mortality, because patients who were expected to die within 48 hours of CAMERA2 trial screening and those with treatment limitations precluding use of antibiotics were excluded. In the setting of MRSA bacteremia early mortality (7- or 30-day mortality) may be related to the infection, with longer-term mortality reflective of underlying health status of the individual—supported by our finding of Charlson comorbidity index score being significantly associated with mortality [10]. Lengthening the follow-up period beyond 3 months after the bacteremia allows inclusion of deaths not directly related to the SAB [27]. However, it is unclear if these indirect deaths are entirely due to underlying conditions, or relate to downstream consequences of the bacteremia, such as endothelial dysfunction and consequent cardiovascular events. Relative survival in patients hospitalized with sepsis showed excess all-cause mortality for at least 2 years following the index admission [28].

Table 3. Association Between Clinical Covariates and Mortality

Variable	Died		Total	HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
	Yes (n = 123)	No (n = 137)					
Sex							
Male	83	86	169	Ref		…	
Female	40	51	91	0.8 (.55–1.17)	.25	…	
Age, y, median (IQR)	74 (63–82)	56 (42–70)	260	1.5 (1.30–1.65)[a]	<.001	1.23 (1.06–1.43)[a]	.008
Country							
Australia	70	117	187	Ref		Ref	
Israel	28	10	38	3.09 (1.98–4.80)	<.001	2.93 (1.80–4.78)	<.001
Singapore	25	10	35	2.43 (1.53–3.85)	<.001	1.96 (1.22–3.17)	.006
Treatment arm							
Combination	65	64	129	Ref		…	
Standard	58	73	131	0.84 (.59–1.19)	.33	…	
CCI score, median (IQR)	6 (5–8)	2 (1–5)	260	1.2 (1.14–1.26)	<.001	1.12 (1.04–1.21)	.002
Pitt bacteremia score							
≤2	78	99	177	Ref		…	
≥3	45	38	83	1.46 (1.02–2.12)	.04	1.48 (1.00–2.18)	.048
SOFA score							
0	25	63	88	Ref		…	
1–2	46	51	97	1.92 (1.18–3.13)	.009	1.31 (.76–2.24)	.33
3–4	30	14	44	3.16 (1.86–5.39)	<.001	1.42 (.72–2.81)	.31
≥5	22	9	31	5.51 (3.09–9.82)	<.001	3.37 (1.76–6.46)	<.001
Baseline creatinine, μmol/L, median (IQR)	120 (74–198)	76 (61–103)	248	1.08 (1.05–1.12)[b]	<.001	1.05 (1.00–1.10)[b]	.045
AKI in CAMERA2[c]							
No	99	112	211	Ref		…	
Yes	24	25	49	90 d: 1.34 (.83–2.20)	.23	…	
				6 mo: 1.24 (.78–1.95)	.92		
				1 y: 1.04 (.64–1.68)	.88		
				2 y: 0.73 (.33–1.61)	.44		
				3 y: 0.52 (.15–1.73)	.28		
Persistent bacteremia[c,d]							
No	102	119	221	Ref		…	
Yes	13	18	31	90 d: 1.34 (.73–2.48)	.34	…	
				6 mo: 1.14 (.64–2.06)	.65		
				1 y: 0.82 (.38–1.76)	.61		
				2 y: 0.43 (.10–1.90)	.26		
				3 y: 0.22 (.02–2.29)	.21		
RRT during CAMERA2[e]							
No	118	134	252	Ref		…	
Yes	5	3	8	1.86 (.76–4.54)	.18	…	

Data are presented as No. unless otherwise indicated.

Abbreviations: AKI, acute kidney injury; CAMERA2, Combination Antibiotic Therapy for Methicillin-Resistant *Staphylococcus aureus*; CCI, Charlson comorbidity index; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; RRT, renal replacement therapy; Ref, reference group; SOFA, Sequential Organ Failure Assessment.

[a]HR reflects a 10-year increase in age.

[b]HR reflects a 25-unit increase in creatinine.

[c]This univariable model uses a time-varying covariate. For HR and *P* value without the time-varying covariate, see the Supplementary Materials.

[d]Bacteremia for 5 days or longer.

[e]RRT needed at any time in the 90 days after CAMERA2 randomization.

The finding of a lack of statistical association between AKI and mortality is surprising. Although our findings appear inconsistent with previous reports, AKI is a heterogenous clinical condition and the AKI phenotype (severity, time to reversal, recurrent injuries) likely influences kidney recovery and progression to adverse health outcomes [29]. The majority of AKI in the CAMERA2 trial (53%) was mild (Kidney Disease: Improving Global Outcomes [KDIGO] stage 1) [5]. The survival curves for AKI have significant uncertainty as demonstrated by the wide CIs.

Although AKI was not associated with mortality, baseline creatinine was associated with mortality on univariate and multivariable analysis. Baseline creatinine at the time of trial enrollment could reflect an early AKI due to the bacteremia or related complications (eg, hypotension), or underlying chronic renal impairment. An increased short-term mortality has been

described in a cohort of patients with chronic kidney disease (not requiring hemodialysis) and SAB, with 46.5% (20/43) dying within 90 days of bacteremia onset [30].

There are limitations associated with our research. In this analysis the cause of death was not available, so its relationship to the index infectious episode cannot be proven. To minimize patient inconvenience and facilitate site participation, only routinely collected data were used. Because of this, we were unable to confirm the GFR reduction at a second time point as recommended in international consensus definitions [7]. Despite using routinely collected data, missing data were minimal. Small patient numbers for some variables may have diminished statistical power. More granular data about the AKI (severity and duration) were not available. Only very few patients progressed to kidney failure, making robust statistical analysis related to this outcome difficult.

Our analysis noted the significant effect of age, with age of 65 years or older increasing the risk of mortality by >3-fold. This has been previously reported by Yahav et al, who noted that SAB in people >65 years of age has a dire 3-year survival rate [18]. These patients require close monitoring over the months following the acute episode; the poor prognosis associated with an episode of SAB should alert healthcare professionals to identify modifiable risk factors and optimize management, aiming to limit downstream mortality.

Further research is needed into the characteristics of the AKI, to determine if mortality risk is higher in patients with more severe AKI, or if the AKI does not resolve within 7 days. Despite lack of an association with outcomes in this analysis, prevention of AKI remains valuable, and improved prediction and early diagnosis of AKI are needed. Finally, the relative nephrotoxicity and efficacy of antistaphylococcal drugs and their exposure–response relationships need to be better defined. The highly anticipated *Staphylococcus aureus* Network Adaptive Platform (SNAP) trial is currently recruiting and will provide information of efficacy of antistaphylococcal therapies [31].

In conclusion, patients with MRSA bacteremia have a high risk of dying within 3 years. Neither AKI nor combination antibiotic therapy were associated with longer-term adverse outcomes in this analysis.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Conceptualization: J. S. D., S. Y. C. T., and A. L. Data curation: A. L., A. S., V. D., C. X., J. O. R., H. F., A. R. T., N. B., A. G., S. D. G., Y. D. B., G. M., N. G., K. S., A. P. R., R. D., Y. L., T. C., Y. H. P., S. S., M. S. W., S. K., and C. T. Methodology: J. S. D., S. Y. C. T., A. L., J. D., J. A. R., M. A. R., A. C., and N. M. Supervision: D. Y., M. P., D. L., R. L., B. R., M. O., N. E. H., S. A., S. K., and N. J. Statistical analysis: A. L., J. S. D., and N. M. Original draft: A. L., S. Y. C. T., and J. S. D. Writing–review and editing: all authors.

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Data availability. The dataset used in the current study is available from the authors in anonymized format upon reasonable request.

Patient consent. Ethical approval was obtained for all other sites contributing data as an amendment to the CAMERA2 trial at relevant Human Research Advisory Committees, using written patient consent from the CAMERA2 trial.

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