Electronic Alerts for Acute Kidney Injury Amelioration (ELAIA-1)

NCT Title and ID: Optimizing Electronic Alerts for Acute Kidney Injury

NCT02753751

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Supplementary Methods

Trial Design and Oversight

A detailed description of the trial design and rationale was previously published.[1] Briefly, we conducted an individual level, parallel-group, randomized controlled trial of AKI EHR alerts versus usual care in hospitalized adults. While patients and providers could not be masked to the intervention, study investigators and analysts were masked to study group assignments until data collection and primary analysis were complete.

The trial was conducted in accordance with the principles of the Declaration of Helsinki and two institutional review boards associated with the six study hospitals approved the study that was deemed minimal risk. Patients were enrolled under a waiver of informed consent, as the alert was deemed unlikely to infringe on patient welfare and informing patients of their AKI diagnosis would contaminate the usual care group. An external data and safety monitoring board performed four independent assessments during the trial, including one formal interim analysis. This trial was registered with clinicaltrials.gov under registration number NCT02753751 prior to study initiation.

Patients

Inpatients adults ≥ 18 years with AKI as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) as an increase in creatinine 0.3 mg/dl within 48 hours or 1.5 times the lowest measured creatinine within the prior 7 days of hospitalization were eligible. We did not use creatinine values >7 days prior to admission in order to avoid including patients with rapid progression of chronic kidney disease, but not AKI. Due to missing and inaccurate urine output data, urine output was not used to classify AKI. Inpatients were enrolled at 6 hospitals within a large health system (Box 1). Hospitals 1 and 2 share personnel, as do hospitals 5 and 6. Hospitals 3 and 4 are largely independent in terms of staffing. The hospitals range from 60 – 1030 beds. Hospitals 1-3 are urban, academic teaching hospitals.

Hospital 4 is a suburban teaching hospital, and hospitals 5 and 6 are suburban, non-teaching hospitals. Patients with a history of end-stage renal disease (based on ICD-9 and 10 codes), a dialysis order in the past year, or an initial hospital creatinine > 4.0 mg/dl were excluded automatically by the AKI detection algorithm. The algorithm, built into the EHR, identified patients with the appropriate creatinine increase who met the above criteria, randomized them (using a simple randomization scheme), and enrolled them into the trial. We subsequently excluded patients whose admission date was prior the "go-live" date of alerts at a study hospital, whose first alert occurred after hospital discharge, who had been enrolled in a prior encounter, and who were enrolled during a two-week period in which alerting ceased due to an upgrade of the electronic health record system. We additionally excluded one patient who was enrolled in both arms of the study: review of the alerting system showed that two individuals opened that patient's chart at the exact same second, leading to the double-enrollment (Figure S1).

Eleven patients were determined not to have AKI after enrollment. On chart review, this occurred due to lab errors in creatinine measurement which allowed them to meet AKI criteria and be enrolled, but the creatinine values were subsequently corrected to lower values that no longer met the AKI definition. We include them in the analysis as these false-positives are likely to occur in broader alert settings.

Intervention

The intervention was an automated, electronic, "pop-up" alert which fired whenever the patient's electronic chart (Epic Systems, Verona WI) was opened (Figure 1). Alerts were displayed only to individuals who had authority to change or enter new orders on behalf of the patient – hereafter referred to as "providers" – which included interns, residents, fellows, attending physicians, nurse practitioners and physician's assistants. Alerts were displayed each time the chart was opened, provided the patient continued to meet criteria for AKI. However, if the provider clicked on any button in the

alert except “dismiss”, the alert would be suppressed for 48 hours for that particular provider. If multiple providers used the EHR to care for the same patient, each of them separately received the AKI alert when they opened the patient chart. Patients randomized to the usual care group generated “silent” alerts which did not display to providers but were tracked, allowing the study team to observe which types of providers opened the chart and how often.

The alert contained an option to add AKI to the patient’s problem list, as well as a link to an AKI order set (Supplemental Figure S2); the set included options for blood and urine testing and renal imaging, but were limited to tests and procedures considered minimal risk (ie IV fluid administration was not included). Providers at each of the study hospitals received education regarding AKI and the AKI alert system prior to study rollout during departmental conferences. Educational content was standardized and included the following elements: the definition and clinical relevance of AKI, the rates of best practice completion after AKI has developed, the study design, and how to interact with the alert (specifically focusing on the consequences of “accepting” or “disagreeing” with the alert. There was no formal curriculum on how to treat AKI in various situations, but providers were reminded of best practices such as urinalysis, urine output monitoring, AKI documentation, and subsequent creatinine measurement.

The development of the alert was an iterative process which used focus groups of providers to give feedback on design elements and wording as well as incorporating suggestions from the IRB. Providers were asked what relevant information should be shown in the alert, what responses could be given, and what elements should appear in the AKI order set (although, due to IRB restrictions, no drug or fluid interventions could be included). They were also asked about alert behavior such as the appropriate “lockout” – how long the alert should be repressed after a provider interacts with it. The final alert was presented to our local Best Practice Alert committee who provided formal approval. The alert was then piloted in “silent mode” for several months for quality assurance. During this time, no

alerts were displayed, but patient data was captured to ensure they met the inclusion / exclusion criteria and to gather data around alert frequency. Once the system was demonstrated to be working correctly, with approval from the BPA committee, the trial was started.

Outcome Measures

The primary outcome was a composite of inpatient AKI progression, receipt of dialysis, or death within 14 days of randomization. AKI progression was defined as reaching a KDIGO creatinine stage higher than the stage present at randomization. Stages 2 and 3 AKI are defined as an increase in creatinine level by 2–2.9 times and an increase ≥3 times baseline, respectively. Receipt of dialysis was also considered to be AKI progression. Patients discharged in the 14-day outcome period were assumed to not meet any of these outcomes had they not met them at the time of discharge. Pre-specified secondary outcomes included the components of the primary outcomes and rates of various AKI care practices. These practices included administration of contrast, fluids, or a nephrotoxic agent (an NSAID, ACE inhibitor / angiotensin receptor blocker or aminoglycoside), ordering of a urinalysis, documentation of AKI, monitoring of creatinine and urine output, and ordering for a kidney consult. An assessment of per-hospital alert effects was also pre-specified.

Data Collection

Data were collected electronically from the electronic health record using a centralized data warehouse (Joint Data Analytics Team, Yale New Haven Health System). Data collected included admission characteristics, time-updated hospital location, laboratory data, medication exposures, vital signs, comorbidities (based on ICD-10 administrative coding) and hospital disposition. Cost information was obtained from a separate database. Direct costs reflect those associated with direct patient contact involving billable services (for example lab, nursing costs, and supplies). Total costs also include non-

billable support services such as medical records, human resources, accounting, support staff, utilities and dietary costs.

Statistical Analysis

We present descriptive statistics as median (interquartile range) for continuous variables and proportions for categorical variables. For the primary analysis, and all comparisons of categorical variables between the intervention and control group, we used the Mantel-Haenszel test, accounting for each hospital site as an individual stratum. The Mantel-Haenszel approach was used to obtain the pooled relative risks across hospital strata without adjusting for other baseline factors. As a sensitivity analysis, we used modified Poisson generalized estimating equations with a robust variance estimator to present the relative risk estimates adjusting for the following characteristics assessed at the time of randomization: age, sex, race, creatinine, blood urea nitrogen, white blood cell count, heart rate, respiratory rate, systolic and diastolic blood pressure, CHF, hypertension, diabetes, modified SOFA score, Elixhauser comorbidity score, and hospital.[2-4] We used the Van Elteren test to compare continuous variables across the intervention groups, again accounting for hospital strata. To compare time-to-event between study groups, we used Cox proportional hazard regression with intervention as the independent variable, stratified by hospital, with censoring at 14-days after randomization. For individual hospital analyses, Kaplan-Meier curves were generated and log-rank tests were used. Patients discharged prior to 14 days without an outcome of interest were assumed to be free of that outcome at 14 days. Death was treated as a censoring event in analyses where death was not the outcome. We used Schoenfeld residuals to examine the proportional hazards assumption in Cox models; there were no violations.

We prespecified several secondary outcomes and subgroup analyses which we present without adjustment for multiple comparisons. We also pre-specified that each hospital would be analyzed

independently for evidence of heterogeneity of alert effects. Given the observed heterogeneity of effects, we explored mediators of that heterogeneity through the use of a generalized linear model in which the independent variables included an alert-by-hospital-type interaction term. Patient-level covariates were then added to this base model to determine if the significance of the interaction would be ablated by including these factors. Although patient characteristics did not account for the heterogenous results, grouping hospitals into into "teaching" vs. "non-teaching" did.

Due to the unexpected finding of increased harm from the alert at non-teaching hospitals, we conducted several *post hoc* analyses, which are specifically identified in the results. To determine if the effect was mediated by actions downstream of the alert, we performed a formal mediation analysis using the method of Baron and Kenny (adjusted for age, sex, race, creatinine, blood urea nitrogen, white blood cell count, heart rate, respiratory rate, systolic and diastolic blood pressure, CHF, hypertension, diabetes, malignancy, modified SOFA score and Elixhauser comorbidity score at the time of randomization) of the following hypothesized mediators: markers of fluid overload, certain medications, the presence of renal consult, attending involvement in the care of the patient (as measured by the percent of alerts that went to attendings versus other providers), and the burden of other interruptive alerts (such as those for sepsis or medication interactions).[5,6] The burden of other interruptive alerts was quantified as the number of other alerts received while the patient was eligible to be receiving AKI or Control alerts, divided by the amount of time they were eligible, leading to an average "non-aki alert per day" metric. Finally, we examined the rates of death and AKI progression in the time period 2 years prior to the start of the trial in each hospital to assess the degree of contamination across the study arms.

We assessed whether alert effectiveness changed over time by including an interaction term representing "time from first enrollment at this hospital" with the randomization status in a logistic regression equation. A significant p-value for this interaction term would suggest that the effect of the alert waxed or waned over time once it was "live" at a given hospital.

Our preliminary data suggested that 24.5% of patients would experience the composite outcome. We determined that a relative 20% reduction in this outcome (to 19.6) would be clinically significant. A sample size of 2,512 in each arm of the study achieves 90% power to detect this degree of change, but given the potential for contamination across study arms (whereby clinicians "learn" to identify and care for AKI over the course of the trial), which would tend to bias the results towards the null, we inflated the sample size by 20% to a total of 6,030.

A single interim analysis was conducted at 50% enrollment to assess for benefit or harm of the alert. An independent Data and Safety Monitoring board (who were unblinded to study assignment) were given guidelines to terminate the study if the p-value associated with interim analysis was <=0.001 for efficacy or <=0.005 for harm. They also had the authority to terminate the study of their own accord regardless of those recommendations. They recommended the study continue at the interim assessment.

Statistical tests were conducted in Stata (v 15.1, College Station TX), SAS (v 9.4, SAS Institute, Cary, NC) and R (RStudio version 1.2.5033 (R version 3.5.3), Boston, MA) and a p-value of <=0.04 was considered statistically significant for the primary outcome (to account for the interim analysis).

We do not report P-values for secondary and exploratory analyses, except in the case of safety outcomes, but report 95% confidence intervals in all cases. The widths of the 95% confidence intervals have not been adjusted for multiplicity and inferences drawn from these may not be reproducible.

Box 1

Characteristic	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Hospital 5	Hospital 6
Location	Urban	Urban	Urban	Suburban	Suburban	Suburban
Bed Count	1030	511	383	206	280	60
Academic	Yes	Yes	Yes	Yes	No	No
Interns / Residents	826 (Shared)		117	23	1 (pharmacy)	0
Patients Enrolled	2515	1248	935	503	684	146
Median (IQR) SOFA Score at Randomization	2 (1 – 4)	1 (1 – 2)	2 (1 – 4)	2 (1 – 3)	2 (1 – 4)	2 (1 – 3)
Median (IQR) Elixhauser Comorbidity Score at Randomization	6 (4 – 8)	6 (4 – 8)	7 (5 – 9)	6 (4 – 8)	7 (5 – 8)	7 (5 – 8)

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