Linking Lab and Pharmacy: Clinical Decision Support to Manage Inpatient Hyperkalemia

BY

SHENGSHENG YU

B.S. in Pharmacy, Zhejiang University, P.R. China, 2006

M.S. in Pharmacy Administration, University of Illinois at Chicago, Chicago, IL, 2009

THESIS

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Defense Committee:

Bruce Lambert, Chair and Advisor
William Galanter, Clinical Medicine & Pharmacy Practice
Stephanie Crawford
Donald Hedeker, Biostatistics
Todd Lee, Pharmacy Practice

This dissertation is dedicated to my parents, Aiming Ding and Mingde Yu. Without your continuous and unrequited support, I would never have gone this far.

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LIST OF ABBREVIATIONS

ACE	Angiotensin-converting-enzyme
ADE	Adverse drug event
AHA	American Hospital Association
AHRQ	Agency for Healthcare Research and Quality
AMIA	The American Medical Informatics Association
ARRA	The American Reinvestment and Recovery Act
CDS	Clinical decision support
CMS	Centers for Medicare and Medicaid Services
CPOE	Computerized physician order entry
CrCl	Creatinine clearance
EHR	Electronic health record
EKG	Electrocardiogram
EMR	Electronic medical records
ESRD	End stage renal disease
GLIDES	Guidelines into Decision Support
HHS	The Department of Health and Human Services
HIT	Health information technology
HITECH	Health Information Technology for Economic and Clinical Health Act
HR	Hazard ratio
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
K-sup	Potassium supplementation
[K+]	Serum potassium level
MDDS	Medical Diagnostic Decision Support
NSAID	Non-steroidal anti-inflammatory drug

LIST OF ABBREVIATIONS (continued)

NQF	The National Quality Forum
ONC	Office of the National Coordinator for Health Information Technology
SPS	Sodium polystyrene sulfonate
UIMC	University of Illinois Medical Center
UIH	University of Illinois Hospital

SUMMARY

Clinical decision support (CDS) has been utilized to link laboratory and pharmacy data to optimize medication therapy. It is shown to improve the quality and safety of heath care only when it is "appropriately implemented." The implementation of CDS is a complicated process that involves complex logic building for the clinical rules and iterative testing and modification to integrate with local work flow. Therefore, this study was conducted to evaluate clinicians' responses to the presence of hyperkalemia before and after implementing laboratory-pharmacy decision support in an inpatient setting. Additionally, efforts were made to explore the factors that might be associated with the changed time course of responses, including patient characteristics, severity of hyperkalemia, renal function, repeated alerts, location of the patients, and alert time. Two hyperkalemia related laboratory-pharmacy CDS rules were implemented at University of Illinois Hospital (UIH), a 450-bed urban teaching hospital in a major academic health center, in June 2003. The synchronous CDS alerted clinicians of abnormal serum potassium level ([K+]) at the time of prescribing ACE inhibitors, angiotensin II receptor Blockers (ARBs), potassium supplementation (K-sup), and potassium-sparing diuretics; while the real-time asynchronous CDS notified clinicians when abnormal potassium results came back while patients were still on the medication. In May 2010, another once-daily asynchronous drug-laboratory alert report was implemented to detect any abnormal potassium test result missed and not acted on after the real-time asynchronous alert.

The assessment of synchronous and real-time asynchronous CDS alert was conducted through a retrospective analysis of electronic health record (HER) data collected from regular clinical care encounters. Clinical actions treating hyperkalemia for patients taking ACE inhibitor and ARB were identified through patient chart review using the pre-identified action repertoire. Canceling the K-sup order and/or repeating [K+] were expected to be the clinical actions to treat hyperkalemia in patients taking K-sup.

SUMMARY (continued)

The effect of synchronous CDS alert was measured by the clinicians' compliance with the synchronous alert, or in another words, the order cancellation rate after CDS implementation. The alert rate of asynchronous alerts during the post-intervention period was compared with the rate of potential asynchronous alert during the pre-intervention period as the indirect measure of the synchronous alert. The effect of the real-time asynchronous alert was measured by time to the first action (clinicians' action time), and patient time to normal [K+]. Total patient time on K-sup normalized by total patient admission days during the same period and also the patient time on K-sup while [K+] ≥ 5.0 mEq/L normalized by total patient time on K-sup were used to measure the combined effect of both alerts on K-sup users. Besides descriptive statistic analysis of the dependent and independent variables, Cox proportional hazards model was used to assess the modulators of clinician's action time and patient time to normal [K+], and the segmented regression analysis was conducted to evaluate the effect of CDS alerts.

On average, the clinicians' compliance with the synchronous alerts was 88.31% for [K+]↔ACE/ARB and 69.46% for [K+]↔K-sup. As the indirect effect of the asynchronous CDS alerts, the alert rate of the real-time asynchronous CDS for [K+]↔K-sup dropped significantly after CDS implementation (28.8% vs. 30.4%, $p = 0.005$). The change in alert rate was not significantly for [K+]↔ACE/ARB (12.1% vs. 12.5%, $p = 0.752$).

For [K+]↔ACE/ARB alerts, the Cox proportional hazards regression results showed, after controlling for all the covariates, the action time did not change significantly after CDS implementation. The clinicians' action time decreased as patient [K+] level increased (HR = 1.51 with $p = 0.003$ for 5.7 mEq/L ≤ [K+] ≤ 6.0 mEq/L, and HR = 1.87 with $p < 0.0001$ for [K+] ≥ 6.1 mEq/L). Alerts from ICU patients were responded more promptly than patients from general medical or surgical units (HR = 1.38, $p = 0.032$). However, the action time was not associated patient age, gender, ethnicity, creatinine clearance level, time of the alert, and whether being

SUMMARY (continued)

the first hyperkalemic episode during the admission. Patient time to normal [K+] also decreased as alerting [K+] level increased (HR = 1.48 with p = 0.003 for 5.7 mEq/L ≤ [K+] ≤ 6.0 mEq/L, and HR = 1.73 with p < 0.0001 for [K+] ≥ 6.1 mEq/L). It took less time for patients with normal creatinine clearance level than those with impaired renal function (HR = 1.71, p = 0.002), but not significant longer for patients with severe renal insufficiency (HR = 0.90, p = 483). Patient time to normal [K+] was also longer if the patient had previous hyperkalemic episode during the hospital stay (HR = 0.40, p = 0.002). Alerts from ICU patients and alert time between 5pm and midnight were also significantly associated with decreased time to normal [K+]. However, patient age, gender, and ethnicity had no effect on the patient time to normal [K+].

The insignificant segmented regression coefficient estimates (p = 0.196 for the difference in the intercept, p = 0.158 for the difference in the slope) confirmed that the real-time asynchronous CDS alerts implemented in June 2003 had no effect in reducing the clinicians' action time when managing hyperkalemia among ACE/ARB users. After controlling for the covariates, the segmented regression results indicated that asynchronous alert did not help to reduce patient time to normal [K+] for ACE/ARB users either (p = 0.134 for the difference in intercept, p = 0.487 for difference in the slope).

For [K+]↔K-sup alerts, the Cox proportional hazards model showed that [K+] level ≥ 5.4 mEq/L and having unknown ethnicity were associated with decreased action time till K-sup cancellation. Aged between 45 and 64 years as compared to 65 years and older, being female, having normal creatinine clearance level, not being the first hyperkalemic episode, being alerted on multiple K-sup orders, and alert time outside of normal day shift were associated with prolonged action time until K-sup cancellation. When counting repeating [K+] as another action, aged 20-44 years and 45-64 years were both associated with shortened action time as compared to aged 65 and older. Being male, having [K+] higher than 5.3, having normal renal

function or severe renal insufficiency, and being the first alert during the admission and located in ICU were significantly associated with shorter action time. It was worth noting that it took longer time to respond to alerts fired between midnight and 7am (HR = 0.48, $p < 0.0001$), but shorter respond time for alerts fired between 5pm to midnight (HR = 1.54, $p < 0.0001$).

The multivariate segmented regression results showed that neither the difference in intercept nor the difference in the slope was statistically different, which indicated that the real-time asynchronous alerts had little effect in reducing time to K-sup order cancellation or time to K-sup order cancellation or repeating [K+]. For patient time to normal [K+], the positive and significant slope for the pre-intervention period suggested an upward trend before CDS implementation (coeff. = 1.69, $p = 0.024$). Even though the asynchronous alert did not decrease patient time to normal [K+] immediately after implementation ($p = 0.588$), there was a significant difference in the slope (coeff. = -2.50, $p = 0.019$). This indicated not only a reduction in outcome, but also a declining trend during the post-intervention period since the post-intervention slope estimate was negative. As the combined effect of synchronous and real-time asynchronous alert, there was no significant change in the monthly patient time on K-sup per patient admission days or monthly patient time on K-sup while [K+] was elevated per patient days on K-sup after alert implementation.

Based on the distribution of [K+] level for inpatients at UIH during the period of January 2009 – June 2009, the cutoffs of ≥5.1 mEq/L and ≥5.5 mEq/L were chosen for the once daily report of [K+]↔K-sup and [K+]↔ACE/ARB, respectively. The time analysis of the [K+] posting time suggested that the best time to run the daily report would be between 9am and 10am to capture most of the hyperkalemic cases if not attended already, and minimize patient time in danger as [K+] was elevated. After discussion with the pharmacy department and the clinical safety team, the time of 2pm was chosen given the workflow of the existing practice. During the

SUMMARY (continued)

period of June 28th 2011 – October 3rd 2011, the once daily report fired 51 [K+]↔ACE/ARB alerts on 34 patients, and 44 [K+]↔K-sup alerts on 32 patients. This equaled to 0.56 [K+]↔ACE/ARB alerts and 0.45 [K+]↔K-sup alerts per day for a 450-bed hospital like UIH.

The multivariate segmented regression analysis indicated that there was no significant decrease in the action time to K-sup cancellation immediately after the implementation of once daily report in May 2010. But there was a gradually descending trend given the significant coefficient estimate for the difference in the slope and the negative slope for the post-intervention period. For the action time to K-sup cancellation or repeating [K+], the segmented regression estimates did not confirm the ascending trend for the pre-intervention period, but did ascertain the impact of once daily report in gradually reducing time to either cancel the K-sup order or repeat [K+]. Moreover, the once daily report did not impact patient time to normal [K+] ($p = 0.752$ for the difference in the intercept, $p = 0.088$ for the difference in the slope). The segmented regression analysis also suggested that the once daily report did not have influence in shortening patient time on K-sup after normalized on total patient admission days. There was a marginally significant drop in monthly average for patient time on K-sup while [K+] was elevated. But the effect could not be affirmed due to poor model fit.

In sum, clinicians complied with synchronous CDS alerts in managing hyperkalemia in inpatient settings. The real-time asynchronous alert failed to demonstrate its effect in accelerating clinicians' action, but had potential effect in improving patient outcomes for K-sup users. The once daily report was effective in detecting potentially hazardous situations that had not been corrected after real-time asynchronous alert. But its impact on changing clinicians' practice behavior and improving patient outcomes was difficult to establish given the rare alert rate.

1. INTRODUCTION

1.1 Background

"… A 77-year old mildly hypertensive woman with no underlying renal disease was admitted to the Emergency Department in a comatose state with fever. The patient had been on low dose enalapril and a potassium rich diet. Five days before admission, rofecoxib, a new selective COX-2 inhibitor nonsteroidal anti-inflammatory drug, was added for leg pain. She was found to have severe hyperkalemia and died 90 min after her arrival…"[1]

Failure to take into account therapeutic drug levels, biochemical and physiologic parameters when making drug choice and dosing decisions, or improperly monitoring those parameters over time, can result in prolonged hospital stays and severe iatrogenic injuries.[2] The importance of linking laboratory data and medication data has been well acknowledged by clinicians in detecting and preventing medication errors related to laboratory parameters.[3-7] However, until recently substantial technology barriers obstructed such linkages.[5, 8] At present, the prevailing adoption of health information technology (HIT) in the health care system enables clinical decision support (CDS) systems to link laboratory and medication data electronically and generate alerts and reminders to support clinical decision making.[9]

Whether being incorporated within the computerized physician order entry (CPOE) systems or being used alone, CDS systems have shown great promise in improving health care. They have helped to improve clinicians' performance,[10-12] prevent medication errors and adverse drug event (ADE),[13-15] support the practice of evidence-based medicine,[16-19] and reduce health care cost.[20-22] Acknowledging all the benefits brought by the HIT, the American Reinvestment and Recovery Act (ARRA) of 2009 allocated $22 billion for promoting adoption

and meaningful use of HIT in the United States.[23] Under ARRA, the Health Information Technology for Economic and Clinical Health (HITECH) Act authorized incentive payments through Medicare and Medicaid to hospitals and clinicians to use certified electronic health record (EHR) systems to achieve the specified objectives.[24] In July 2010, the Centers for Medicare and Medicaid Services (CMS) released the final rules to support the "meaningful use" of EHR. The requirement of enabling qualifying EHR to "implement one CDS rules relevant to specialty or high clinical priority along with the ability to track compliance with that rules" must be met in order to qualify for the incentive payments.[25]

The University of Illinois Medical Center (UIMC) has been at the forefront of HIT deployment since its early adoption of EHR in 1999.[26] Thereafter, experts have been conducting HIT assessments and integrating research findings into clinical practice.[27-32] These empirical and evidence-based experiences provide UIMC with a unique opportunity to examine the impact of HIT from early stage development to mature application.

1.2 Statement of the Problem

CDS only improves the quality and safety of health care when it is "appropriately implemented."[33] The implementation of CDS is a complicated process that involves complex logic building for the clinical rules and iterative testing and modification to integrate with local work flow. While there has been considerable attention devoted to the implementation of CDS in the EHR systems since the 1990s,[24, 34-36] the above mentioned studies have made the effort to measure the effectiveness of CDS in a short time frame. To the investigator's knowledge, no longitudinal assessment has been conducted in individual institutions to evaluate the evolving technology since its initial adoption, let alone its effect in changing clinicians' practice behaviors and patient outcomes. Beyond the limited findings from those periodic studies, research in

establishing quantitative analytical framework for assessing the success of CDS implementation is still lacking in regard to choosing and evaluating the appropriate outcome measurements and analytical methods.

Even though as many as 45% of medication errors may be related to inappropriate or inadequate laboratory monitoring,[37] CDS on drug-laboratory interaction is less developed compared to those on drug-drug and drug-allergy interactions, probably because it involves important prerequisites in CPOE and an advanced logic-building process.[5, 20] However, there is a lack of rigorous evidence, and most of the knowledge base of drug-laboratory related CDS is based on expert opinions or vague descriptions in package inserts, which poses further difficulty when implementing such CDS systems.[20]

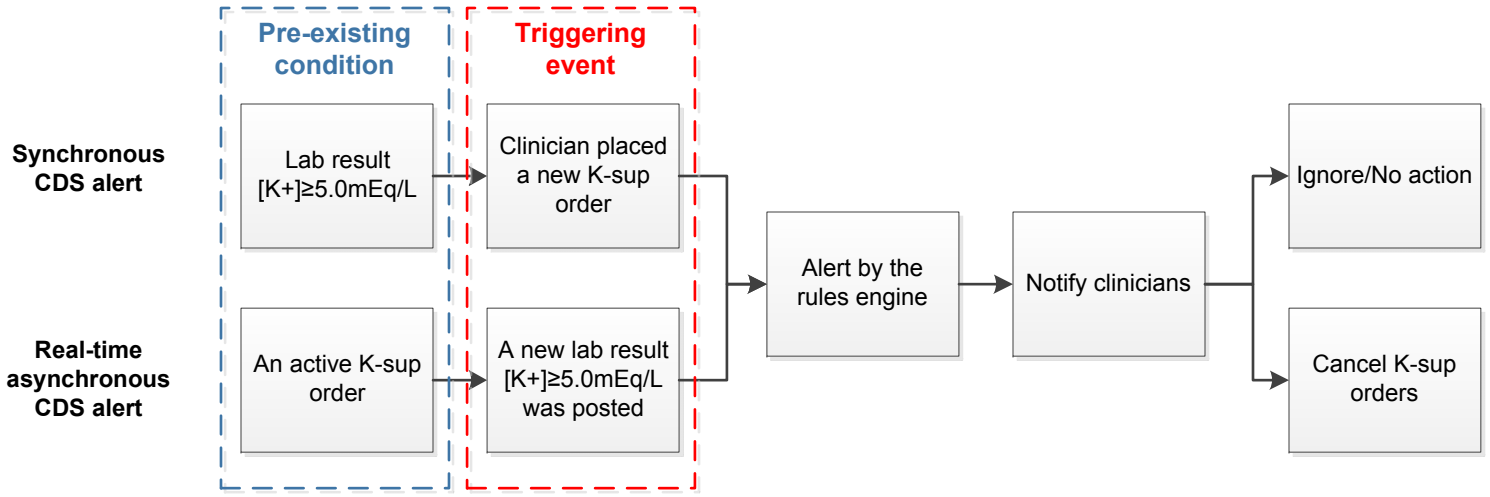
Elevated potassium level in blood, or hyperkalemia, is one of the most frequent laboratory triggers in detecting and identifying adverse drug event and medication errors.[38] It can be caused by use of certain medications, including angiotensin-converting-enzyme (ACE) inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), potassium-sparing diuretics, potassium supplements (K-sup), and trimethoprim.[39] It is reported that hyperkalemia occurs to 10%-38% of hospitalized patients using ACE inhibitors and 10% of outpatients within one year after ACE inhibitor therapy initiation.[40] Despite the potentially life-threatening consequences of hyperkalemia, K-sup were still prescribed in ambulatory settings when patients had elevated serum potassium level ([K+])(≥ 5.3 mEq/L) from recent laboratory testing.[4] Follow-up and repeated testing for critical outpatient results ([K+] ≥ 6.0 mEq/L) is also suboptimal.[41] Besides these findings in outpatients, little has been researched on how hyperkalemia is treated in the complex inpatient settings where timely clinical responses are more critical because patients are more vulnerable.

1.3 Purpose of the Study

This study was conducted to evaluate clinicians' responses to the presence of hyperkalemia before and after implementing laboratory-pharmacy decision support in an inpatient setting. Additionally, efforts were made to explore the factors that might be associated with the changed time course of responses, including patient characteristics, severity of hyperkalemia, renal function, repeated alerts, location of the patients, and alert time. Two hyperkalemia related laboratory-pharmacy CDS rules were implemented at University of Illinois Hospital (UIH) in June 2003. The synchronous CDS alerted clinicians of abnormal [K+] at the time of prescribing ACE inhibitors, angiotensin II receptor Blockers (ARBs), K-sup, and potassium-sparing diuretics; while the real-time asynchronous CDS notified clinicians when abnormal potassium results came back while patients were still on the medication (Figure 1).

In May 2010, another once-daily asynchronous drug-laboratory alert report was implemented to detect any abnormal potassium test result missed and not acted on after the real-time asynchronous alert. The report reviewer, either a hospital pharmacist or a physician, would contact the relevant clinicians if the reviewer believed that medical intervention was needed to address the hyperkalemic situation. One purpose of adding this report to the two existing CDS alerts was to demonstrate that, when integrated properly, this linkage between laboratory and pharmacy data would be a useful safety net to capture signals for potential ADEs. Another rationale for adding this alert was to demonstrate the process of linking laboratory and pharmacy data in a retrospective but efficient way that most of hospitals should be capable of, using the most basic data systems even without advanced CDS or CPOE.

Figure 1. Illustration of synchronous CDS alert and real-time asynchronous CDS alert in the context of managing hyperkalemia during K-sup use



Before those three laboratory and pharmacy linkage CDS were implemented, another communication mechanism also existed to notify clinicians of hazardous laboratory values which "reflect pathophysiological derangements at such variance with normal as to be life threatening if therapy is not instituted immediately."[42] The critical value reporting is required by laws, regulations, and accreditation agencies such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO, currently called the Joint Commission) and the College of American Pathologists in the US.[43-46] However, no regulations have specified the laboratory tests require critical value notification nor the critical value limits for each test.[47] At UIH, any potassium level ≥ 6.1 mEq/L is considered critical, and laboratory personnel are required to contact the responsible clinician immediately once the laboratory results become available.[48]

In order to examine clinicians' reactions to hyperkalemia in sufficient detail while keeping the study in a manageable scope, this study focused only on hyperkalemic cases among inpatients using ACE inhibitors, ARBs, and K-sup.

1.4 Objectives and Hypotheses

This study aimed to evaluate the effect of laboratory-pharmacy linkage CDS on clinicians' practice behaviors and patient outcomes, and to demonstrate the analytical approach for quantitative assessment. To achieve this objective, this study pursued the following four specific aims:

1. Evaluate the effect of synchronous and real-time asynchronous CDS on management of hyperkalemia in inpatients using ACE/ARBs and K-sup.
2. Identify factors associated with the timing of clinical responses.
3. Identify factors associated with patient outcomes.

4. Assess the marginal effect of once-daily reporting on detection of hyperkalemia not otherwise detected or corrected by existing real time alerts.

In order to accomplish these aims, four hypotheses were generated:

Hypothesis 1: Hyperkalemia was managed more efficiently and acted on more promptly after CDS implementation.

Hypothesis 2: Clinicians' action time was associated with the severity of the alert, the alert time, and the patient's renal function.

Hypothesis 3: Patient time to return to normal [K+] was associated with the severity of the alert and patient's renal function.

Hypothesis 4: The once-daily report identified additional cases of hyperkalemia not otherwise detected or corrected by existing real time alerts.

The first three hypotheses were tested separately in patients taking ACE/ARB and K-sup, and Hypothesis 4 was tested only in K-sup patients.

1.5 Significance of Research

This study demonstrated the implementation of three different types of CDS laboratory-pharmacy linkages and the analytical approach required to evaluate their effect in improving clinical practice and patient outcomes. Previous studies on CDS have mainly been conducted in large academic hospitals rather than in smaller community hospitals. With the wide adoption of CDS required by HITECH act of 2009, it is foreseeable that the need to perform this type of quality assessment for CDS systems at different levels will be significant for community hospitals that typically lack adequate manpower or relevant expertise and experience to conduct such studies. Even though this study was conducted in an urban academic teaching hospital, the process of developing the appropriate analytical framework and the practical experience

gained from this study is very valuable and transferable for other medical institutes. Besides that, the detailed technical requirements were also described for the CDS interventions under study, which are of different levels of technical complexity. Thus, applicable findings can be easily identified if they are relevant to the CDS systems used in other institutes.

Besides the evaluation of the CDS, the adoption of EHR in 1999 made it possible to study the trend in clinical practices and the evolving evidence from the past decade at UIH. To the investigator's knowledge, this study was the first one to demonstrate how the CDS was developed and integrated into clinical workflow given the evolving HIT development over the past decade. Thus, lessons and findings from this study would provide hands-on experience and pave the ground for delivering effective laboratory-pharmacy linkage CDS for healthcare organizations, application and knowledge base vendors, policy makers, and researchers.

2. LITERATURE REVIEW AND CONCEPTUAL FRAMEWORK

2.1 Clinical Decision Support

2.1.1 Definition of Clinical Decision Support

The definition of CDS varies by individuals and health organizations given its complexity and multidimensionality. As early as 1991, CDS was defined as "active knowledge systems which use two or more items of patient data to generate case-specific advice."[49] This definition indicates that CDSs are typically designed to integrate a medical knowledge base, patient data, and an inference engine, and to provide patient specific advice to assist clinicians in caring for individual patients. Perreault and Metzger defined CDS broadly as "any automated tool that helps clinicians improve the delivery or management of patient care."[33] This definition excludes those decision support tools that were designed for non-care providers like patients and administrators. Perreault and Metzger also argued that the clinical data captured in its data warehouses enabled CDS systems to perform patient-specific or population-specific retrospective analysis, which could then be used to develop guidelines, critical pathways, and treatment protocols. However, such retrospective approaches were not usually considered as CDS since they were not designed to assist clinicians at the point of care.[50] These distinctions are important because many CDS products were advertised for their decision support capabilities, which may be referred to the decision support to non-care providers or to the retrospective type of support.

Even though a reference book used by a clinician at the time of prescribing can be viewed as one simple form of CDS, CDS now typically refers to a variety of computer-based

systems that were grouped loosely together as part of HIT, in addition to the CPOE systems and electronic medical records (EMRs).[35] There are three common features of CDS systems: 1) a compiled knowledge base that includes, for example, information on diagnosis, drug interaction, and clinical guidelines, 2) a program for combining the knowledge with patient-specific information such as age, weight, gender, renal function, etc., and 3) a communication mechanism to enter patient data into the system and provide relevant information back to the clinician.

According to the CMS Notice of Proposed Rule Making, CDS is described as "health information technology functionality that builds upon the foundation of an EHR to provide persons involved in care processes with general and person-specific information, intelligently filtered and organized, at appropriate times, to enhance health and health care."[51] In this new era of HIT, CDS interventions include but are not limited to alerts and reminders, clinical guidelines, order sets, patient data reports and dashboards, documentation templates, diagnostic support, reference information delivering, and other tools that support decision making within the clinical workflow.

There are also a few terms that are frequently mentioned in the CDS related literature. The rules for CDS can be either active or passive.[20, 52] An active rule is a pre-defined set of circumstances, determined by the integrated clinical information of the patient, that triggers an active alert during the order-entry process.[53] A pop-up window with patient laboratory test result relevant to the medication order being entered is an example of active rule. A passive rule or referential information usually runs in the background or gather information to generate a report without interfering with the clinical workflow.[53] Although sometimes the clinicians may be reminded the existence of certain information, they can choose to access it or continue the workflow without viewing the information. Some authors have categorized active CDS into two stages: basic CDS and advanced ones.[20, 54] Basic CDS includes drug allergy checking, basic

dosing guidance, formulary decision support, duplicate therapy checking, and drug interaction checking. Advanced CDS refers to those that require specific patient information, such as dosing support for renal insufficiency and elderly patients, guidance for medication related laboratory testing, drug-disease contraindication checking and drug-pregnancy checking. CDS can also be categorized as synchronous and asynchronous events and processes. A synchronous event, such as dosing checking, occurs as part of the prescription order entry process; while an asynchronous one like a request for a report, may occur after order entry.[53]

2.1.2 Development of Clinical Decision Support

A large number of CDS systems have been developed over the past 40 years. Most of the early CDS systems can be described as stand-alone expert systems which were aimed to simulate human thinking of an expert clinician when confronted with a patient.[55] Many of the earliest systems were merely for diagnostic decision support. Examples include the CASNET (Causal ASsociational NETworks) developed in the 1960s, the de Dombal's system developed at Leeds University to support the diagnosis of acute abdominal pain and the need for surgery, a rule-based system called the INTERNIST developed at University of Pittsburgh in 1974 for the complex diagnosis in general internal medicine, and the MYCIN that were developed at Stanford University to diagnose and recommend treatment for certain blood infections. Some of the successful systems developed in the 1980s were even commercialized, like DXplain and QMR (Quick Medical Reference).[56] During these early years, these diagnostic CDS were referred to as Medical Diagnostic Decision Support (MDDS) Systems, which deployed clinical algorithms, clinical databanks that include analytic functions, mathematical pathophysiologic models, pattern-recognition systems, Bayesian statistical systems, decision-analytical systems, and symbolic reasoning or "expert" systems.[57] As those system developed, the intent gradually changed to assist the clinicians in their own decision making while the users were expected to

actively interact with the system and filter the useful information as needed.[55] Other applications, including interactive dialogue and structured data entry control, computer-based consultations, incorporation of clinical practice guidelines, and biomedical signal and image processing, were built into CDS.

Behind all the technical and scientific development, there were social, cultural, economic, and governmental influences that contributed to the climate of enthusiasm and drove the deployment of CDS. Greenes summarized the major forces for the development of CDS in the book *Clinical Decision Support: The Road Ahead*.[9] He thought the progress of computer science, cognitive science, artificial intelligence, statistics, and communication technologies were the so-called "technology imperative" that opened up the possibility for CDS and stimulated its development. The practice of evidence-based medicine and the need to find patient-specific and context-specific resources more rapidly in this information-overloaded era created the impetus to implement CDS. Moreover, "the empowerment of patients and consumers for more two-way communication and shared decision-making, recognition of importance of proactive support to prevent medication error, the need for reminders, alerts, recommendations and other functions to foster higher health care quality, the aging population and increased complexity of disease, and wide spread of EMR" also drove the development and implementation of CDS.[9]

In 1991, the Institute of Medicine emphasized in its report that CDS is the major reason for computerizing the patient record.[34] As indicated by supporting research findings, CDS can improve the quality of care, reduce health care costs, and improve patient satisfaction if implemented appropriately.[33] Motivated by the demand to deliver safe and effective care, an increasing number of academic health centers, community-based organizations, and physician groups have been actively implementing CDS into their patient care systems and evaluating its effects on physician performance, patient outcomes, and medication safety.[10, 11, 14, 15, 58-62]

In response to the Office of the National Coordinator for Health Information Technology (ONC) and the Agency for Healthcare Research and Quality (AHRQ)'s request, the American Medical Informatics Association (AMIA) established the CDS roadmap development steering committee to lead federal and private sector activities to advance CDS in 2005.[35] The CDS roadmap committee recognized the lack of a single coordinating entity that oversees strategic development and deployment of CDS tools as the limiting factor for its efficient use. Therefore, the CDS collaboratory, AHRQ, and the Department of Health and Human Services (HHS) started to catalog CDS activities at the federal level. An ad hoc CDS planning group was convened in 2007 under the American Health Information Community and developed a set of recommendations for federal adoption.[35] At the end of 2008, the National Quality Forum (NQF) gathered a group of 28 major organizations and identified a set of national priorities and goals to help guide the performance improvement programs. The NQF also developed the national consensus standards for structure measures for assessing HIT, including e-prescribing, EHR, CDS systems, and CPOE. Later, the promotion of HIT assessment was taken over by the Leapfrog Group, which launched several consortiums and initiatives to foster the development and dissemination of best practices in adopting, implementing, and researching CDS.[35]

The importance of conducting demonstration projects and sharing knowledge was also highly recognized in the development of CDS. In the past three years, AHRQ has been funding CDS-related grants, contracts, and demonstration projects through several initiatives.[35] The two-year Guidelines into Decision Support (GLIDES) project for integrating evidence-based guidelines for pediatric obesity and asthma into ambulatory care practices, the Clinical Decision Support Consortium to bridge different health care sectors, and the Center for Education and Research on Therapeutics at Brigham and Women's Hospital are a few examples of the AHRQ's contribution. The findings were widely disseminated through AHRQ-funded webinars, published reports, toolkits, and numerous resources that are publicly available. Other initiative

groups like Morningside Initiatives, social networking websites like ClinifoWiki, and CDS vendor community also played a role in sharing knowledge and disseminating evidence.[35]

In its federal HIT strategic plan for 2008-2012, the ONC stated its key objectives of privacy, confidentiality and security, interoperability, EHR adoption and collaborative governance which laid a concrete foundation for CDS adoption.[36] One year later, the passage of HITECH Act provided incentives for hospitals and clinics to adopt EHR to achieve the specified objectives.[23] In July 2010, the final rules released by CMS to support the "meaningful use" of EHR generated incentives for implementing CDS rules in qualifying EHR.[25]

Despite the documented evidence on how successful CPOE with implemented CDS is in improving health care quality and efficiency, the adoption rate of EHR is still low both in ambulatory care settings and in acute care hospitals in the United States.[63] A survey of all acute care general medical and surgical member hospitals of American Hospital Association (AHA) reported that, among the 63.1% of responding hospitals, CPOE for medication had only been implemented in 17% of the hospitals. And only 9.1% of them had some form of EHR in use in 2008.[64] Reasons for the delayed progress of EHR adoption include the fragmentation of the U.S. health care system, inadequate incentives for adoption, and problematic work practice integration.[63, 65, 66] Veinot et al.[65] stated that the unintended consequences that accompany with introduction of EHR systems, such as shifts in power relations and work distribution between providers, disruptions in health care communication, and changes in patient care structure, were the critical but underappreciated factors that haltered the wide adoption of EHR. The authors also argued that the conflicts between systems' decision rules and the actual clinical practice could result in poor integration of systems into clinical practice and uncertainties about the ultimate clinical outcomes of EHR deployment.

2.1.3 Goals of Clinical Decision Support and Its Application

The "Five Rights" of CDS states the overall goal of CDS, which is to provide the right information to the right person, in the right format, through the right channel, at the right points in clinical workflow to improve health and healthcare decisions and outcomes.[67] This "Five Rights" approach also sets the four dimensions of CDS that can be used to describe and distinguish different CDS systems: 1) whose decisions are being supported, 2) what information is presented, 3) when is it presented, and 4) how is it presented.[55] Being different in these dimensions, the audience of the CDS can either be physicians, the most common user group, or the nurses or other clinicians, which depends on the efficiency of clinical workflow. The patient information can either be presented immediately at the point of care, or prior or after the patient encounter in order to be less disruptive. The information can either be delivered automatically to the clinicians, or upon request. Besides these three aspects of CDS, the quality of the information being presented and the underlying evidence are the major determinants of the effects of CDS on patient safety and quality improvement.[55] CDS systems can also differ in how much control the users have over the decision when using CDS. Different control levels can be designed into the CDS so that it can only remind clinicians of things they intend to do but should not have to remember, provide information when clinicians are not sure of what to do, correct errors that clinicians have made, or recommend the clinicians to change their plan.

2.1.3.1 Health Care Quality and Safety Improvement

By achieving the "Five Rights", CDS has been able to detect potential problems in patient safety and health care quality and inappropriate utilization of services, medications and supplies. Paralleling the development of CDS, published systematic reviews and meta-analyses have showed fairly consistent evidence that CDS improves clinicians' performance.[10-12] The most recent systematic review published in 2005 reported that CDS systems improved practitioner performance in 64% of the studies (62 out of 97 studies), and the success was most

likely to be achieved using reminder systems (76%).[10] For example, Galanter and colleagues studied the effect of CDS on clinical responses and response time in the management of digoxin therapy, and found that checking for unknown serum values of digoxin, potassium, and magnesium increased significantly after CDS implementation ($p < 0.01$), and electrolyte supplementation increased in response to newly reported hypokalemia and hypomagnesemia.[30] Another study about the use of CDS alerts in reducing inpatient administration of medications contraindicated with renal insufficiency reported an absolute reduction of 42% (from 89% to 47%) for the likelihood of a patient receiving contraindicated drug after alert implementation.[29] However, the evidence on how well these CDS systems help to improve patient outcomes is limited. In the same systematic review, only 7 trials (13%) reported improvements in patient outcomes.[10]

2.1.3.2 Prevention of Medication Errors

When incorporated within the CPOE systems or being used alone, CDS systems can help prevent medication errors. A study published in 1998 showed that CPOE with CDS reduced non-missed-dose medication error rate by 81% ($p < 0.0001$) and non-intercepted serious medication errors that had high potential to cause medication harm by 86% ($p = 0.0003$).[13] A systematic review published in 2003 identified four additional trials assessing CPOE with CDS and seven assessing isolated CDS systems.[14] Two out of the five CPOE trials reported a great reduction in serious medication errors, and four of the seven isolated CDS demonstrated significant improvement in ADEs. Another systematic review identified 10 original studies published between 1966 and March 2007.[15] Five of the 10 studies showed a statistically significant decrease in ADEs ($p \leq 0.05$), four showed non-significant reduction, and one demonstrated no change in ADE rates. These positive but relatively inconsistent conclusions of CDS's effect on preventing ADEs were explained by the poor study design and statistical insignificance.[55] One reason for the mixed findings could be the methodological issues such as

ceiling effects and the low statistical power due to the rarity of ADEs. These two issues could have made the studies difficult to detect statistically significant effects if performance was already good before CDS implementation. Moreover, there are often other intervening factors, like patient compliance and clinicians' ignorance or override, that could have impacted the final outcomes.

2.1.3.3 Support for the Practice of Evidence-based Medicine

CDS has also been shown to support the practice of evidence-based medicine by ensuring the best clinical knowledge and recommendations are utilized by clinicians. Given the rapid pace in the growth of knowledge, making the optimal clinical decision requires the clinicians to have access to a large amount of complex information. Sim and colleagues recommended coupling CDS technology with evidence-based medicine for improving health care quality.[16] They strongly advocated for the so-called "evidence-adaptive CDS systems" that capture the most up-to-date evidence from the research literature and practice-based sources as the clinical knowledge base of the CDS. When bringing these two potentially powerful tools together, CDS has been used to better communicate clinical guidelines to practitioners within clinical workflow. It was reported that standing orders produced by CDS at the time of patient discharge increased influenza vaccination rate from 30% to 42% ($p < 0.001$) and pneumococcal vaccination rate from 31% to 51% ($p < 0.001$) as compared to traditional physician reminder.[17] Another study implemented the deep-vein thrombosis prophylaxis guideline into the CDS and reduced the risk of deep-vein thrombosis or pulmonary embolism at 90 days by 41% ($p = 0.001$).[18] CDS has also been a valuable technology in implementing and validating evidence-based guidelines. Sucher et al. described the use of CDS in specifying and providing best care for trauma patients.[19] They concluded that CDS offers the unique approach to decrease variability, test intervention, and validate improved quality of care when implementing evidence-based guidelines.

2.1.3.4 Reduction in health care cost

Besides the above mentioned clinical benefits, CDS, when incorporated with CPOE systems, has also shown to reduce health care cost.[20] It was reported over the 10-year period from 1993 to 2002, the Brigham and Women's Hospital invested $11.8 million in their CPOE system with CDS, which produced $16.7 million in cumulative net savings and $9.5 million net operating budget savings.[21] Among all the CDS elements implemented, greatest cumulative savings resulted from renal dosing guidance, nursing time utilization, specific drug guidance, and adverse drug event prevention. Another study conducted at the LDS Hospital in Salt Lake City compared the anti-infective agent cost, total hospital costs, and length of hospital stay before and after linking the CDS program with computer-based patient records in assisting the use of anti-infective agents.[22] They found that all three outcomes were improved by significant reduction in drug allergies, excess drug dosages, antibiotic-susceptibility mismatches, and ADEs.

However, these two and other relevant studies bear several common limitations. When estimating the value of CDS, most of the studies focused on the cost saving resulting from shortened length of hospital stay and avoidance of inappropriate prescribing, and used the cost data of prevented ADEs to estimate the cost savings. This cost calculation excludes direct costs saved from the clinical benefits of CDS other than ADE prevention. Moreover, most of the CPOE and CDS systems studied were "home grown" systems that have been developed over many years and most often with external grant support. Thus, it is difficult to estimate the cost of developing the CDS. Most studies used a pre- and post implementation approaches rather than a direct assessment of actual cost savings. Failing to adjust for the changes other than CDS implementation would definitely pose threat to the internal validity of the study.

2.1.4 Challenges and Opportunities for Clinical Decision Support

Obstacles have been presented throughout the development of CDS, ranging from the technical challenges in the earlier years to the difficulty of implementing effective knowledge base and efficient communication channels are faced today. Given the aim of assisting, rather than replacing clinicians, CDS users have the overall control over the final decision. The issue of ignoring the advice of CDS has been shown in a variety of CDS systems, including diagnostic systems, evidence-based treatment recommendation, and alerts for drug interactions.[55] The particular problem of overriding drug interaction alerts has been consistently reported in inpatient, outpatient, and long-term care settings. It was reported that only 1.4% of non-interruptive drug-drug interaction alerts were accepted, and 30.2% of the alerts for drug-drug combinations which could be "potentially serious" were overridden at an outpatient study site.[68] And the override rate for an inpatient site with advanced CDS system and for an inpatient site with basic CDS system were 14.0%, and 44.1%, respectively. There have been a few attempts to address this issue. In situations when CDS recommendations were ignored, patients were sicker or in more complicated condition,[22] or the clinicians had strong beliefs in their choices and no better alternative was available.[52] Other possible explanations include the speed and ease of access,[52, 55] lack [68]of tiering by severity,[62] and alert fatigue.[69] However, none of these explanations have been validated, and cognitive studies on ignoring alerts are still lacking.[70]

Since it is clinicians' decision that directly influence care processes, it is difficult to evaluate the effect of CDS without a fully understanding of why CDS recommendations are ignored. The modulators for clinicians' alert ignorance were categorized as: 1) alert content regarding the quality of clinical knowledge, and 2) alert presentation that has an effect through human factors such as alert display, textual information, and prioritization.[68] An observational study was conducted to identify potential modulators of the acceptance of the drug-drug interaction alert.[68] Factors, including frequency of the alert, quality of display, alert level,

inpatient setting (as compared to outpatient setting), and dose-dependent toxicity, were positively associated with alert acceptance. Patient age was a significant modulator in cancelling the prescription when accepting the alert, but not in modifying the prescription.

Current findings have demonstrated basic computerized systems do not work unless associated with advanced systems like CDS.[71] However, healthcare providers and HIT vendors are still facing great challenges when implementing CDS effectively and efficiently. After systematically reviewing the CDS studies published up to 2003, Kawamoto and colleagues identified several key features of CDS system that were critical in improving clinical practice.[72] They found automatic provision of decision support as part of clinician workflow, provision of recommendations rather than just assessments, provision of decision support at the time and location of decision making, and computer based decision support were the significant predictors of a successful system. These findings were echoed by other experts in the field. Bates and colleagues provided ten commandments from their experiences while developing and implementing CDS systems at Brigham and Women's Hospital.[52] They acknowledged the importance of integrating CDS suggestions with clinical practice and anticipating clinicians' needs in order to provide them with needed information at the time they need. They were aware that clinicians were more likely to resist suggestions unless an alternative was offered, and it was easier for them to change their decision (e.g., dose, route, or frequency of a medication) than stopping their action. They also mentioned that the systems must be developed in a way that made it easy for clinicians to do the right thing by considering human factor principles and through usability testing.

2.2 Empirical Studies Linking Laboratory and Pharmacy Data

Most of the current laboratory-pharmacy CDSs exist in the form of reminders to assist physicians with monitoring medications that have a narrow therapeutic range.[10] For example, a

study showed that anti-epileptic drug levels can be optimized through reminders at the time of ordering, which reduce inappropriate ordering rate from 54% to 14.6%.[73]

Other forms of CDS with direct linkage between laboratory and pharmacy have also been used in outpatient settings. Steele et al. found that automated drug-laboratory interaction alert helped providers increase ordering of appropriate laboratory tests from 39% to 51% ($p < 0.001$) in a primary-care clinic, but no statistically significant difference was observed for ADEs defined by Naranjo score which measures the likelihood of whether an ADE is due to the drug rather than other factors.[74] This positive findings assured the effect of CDS on improving physicians' behavior after Weingart et al. reported that 91.2% of the drug-allergy and 89.4% of high-severity drug-drug interaction alerts were overridden by primary care physicians.[75] But they addressed the negative finding by stating that the alert threshold was too low and alerts should be suppressed for medication renewals that the patient tolerated.

Also conducted in outpatient settings, Schiff et al. found that 1.5% K-sup prescriptions (498 prescriptions over a 1-year period) were written and dispensed for patients with [K+] ≥ 5.3 mEq/L from the most recent test, and 159 prescriptions were written for patients with [K+] ≥ 6.0 mEq/L. The authors identified two errors: 1) prescribing K when most recent [K+] was elevated; and 2) prescribing K-sup when [K+] was elevated on the same day and fail to contact patients to discontinue K-sup. They concluded that, with properly designed systems linking laboratory and pharmacy, these errors should be preventable. The authors also commented that there were no clear recommendations on a serum level above which K-sup should be discontinued. Even though such clinical decisions must be made when taking patients' renal function, diuretic dose, and use of other drugs into account, the upper limit of normal ([K+] ≥ 5.3 mEq/L) would be unwarranted and potentially dangerous in many clinical situations. And once [K+] exceeded 6.0 mEq/L, prompt clinical attention must be given.

In order to identify factors associated with delayed follow-up of severe hyperkalemia in the ambulatory settings, Moore and colleagues examined the medical records of all adult patients with [K+] ≥ 6.0 mEq/L over a 4-year period. They found that 10% of cases had no follow-up, while median follow-up time was 3 days.[41] They also reported that private insurance, taking medications that can cause hyperkalemia, and higher serum potassium level were significantly associated with shorter follow up time. Although these two studies were focused on outpatients, they affirmed that follow-up of abnormal potassium test results was far less than optimal in ambulatory care, and this situation can be improved through communication between the laboratory and pharmacy systems.

2.3 Hyperkalemia

2.3.1 Pathophysiology

Approximately 98% of the total body potassium is stored in the intracellular fluid, while only 2% exists in the extracellular fluid.[76, 77] The Na^+-K^+-ATPase pumps potassium, against its electrochemical gradient, from the extracellular fluid into the intracellular fluid. Hyperkalemia occurs when the intra- and extracellular potassium distribution is disturbed.[39]

Causes for hyperkalemia include excess intake, redistribution from intracellular fluid to extracellular fluid, and impaired renal secretion.[39] Excessive potassium can rarely produce hyperkalemia unless renal potassium secretion is also impaired, whether through drug, renal insufficiency, or other causes. The primary sources for potassium intake are from food and salt substitutes, especially from some fruits and vegetables with high potassium concentration. Another common dietary source of potassium is enteral nutrition supplements and hyperalimentation fluids. Patients with renal failure receiving total nutritional support through enteral nutrition supplements or hyperalimentation fluids should be closely monitored since the contained potassium concentration is usually excessive for patients with renal insufficiency.

Another source for potassium comes from medications that are supplied as the potassium salt (e.g., penicillin and citrate) or the K-sup, such as potassium chloride. K-sup are frequently administered to patients who are also taking diuretics and at risk of hypokalemia. Given the evolving evidence that K-sup can also decrease blood pressure and improve mineral balance and skeletal calcium metabolism in postmenopausal women, it has been prescribed frequently for conditions other than hypokalemia.[78-80] Hyperkalemia could occur frequently among those patients if serum potassium and renal function are not carefully monitored.

Since the vast majority of total body potassium is stored in the intracellular fluid, any small change in the distribution between intra- and extracellular fluid can cause hyperkalemia.[39] Possible causes include acidosis, membrane-depolarizing anesthetics, and extracellular hypertonicity result from “effective osmoles” that generate osmotic pressure. Drugs like insulin, aldosterone, and β-adrenergic agonists that interfere with the hormonal systems can also regulate potassium distribution. When potassium intake increases, aldosterone synthesis also increases to accumulate more potassium in the intracellular compartment. Aldosterone synthesis is regulated mainly by renin-stimulated angiotensin II production. Therefore, drugs that inhibit adrenal aldosterone synthase (e.g., heparin) or angiotensin II-mediated stimulation of adrenal aldosterone synthesis (e.g., β-adrenergic agonists, atrial natrieretic peptide analogues, ACE inhibitors, and ARBs), or inhibit aldosterone action at cellular level (e.g., spironolactone), can all cause hyperkalemia through distorted potassium distribution.

Impaired renal potassium secretion can also induce hyperkalemia due to reduced nephron mass and intrinsic impairment of active potassium secretion.[39] Since the number of collecting ducts is related to the glomerular filtration rate, renal insufficiency or renal failure will result in impaired renal potassium secretion. Many drugs in common clinical use interact with collecting duct in potassium secretion. For example, aldosterone directly increases potassium secretion in addition to its effect on potassium distribution; arachidonic acid metabolites regulate

potassium channels; NSAIDs reduce arachidonic acid metabolite production and decrease potassium secretion through reduced potassium channel; potassium-sparing diuretics and antibiotic trimethoprim and pentamidine block the cell apical sodium channel; and digitalis and its analogue inhibit the cell basolateral Na^+-K^+-ATPase.[39]

2.3.2 Adverse Effects

Hyperkalemia can decrease myocardial cell conduction velocity and increase the rate of repolarization.[81, 82] The decreased conduction velocity induce increases in the PR interval and the width of the QRS complex on electrocardiogram (EKG), while the increased repolarization rate leads to an increased height of T wave which can also be seen as the peaked T waves from the EKG. A slowed conduction velocity, especially with peaked T waves, increases the likelihood of ventricular fibrillation, which can lead to sudden death. Correlation between the EKG findings and the severity of hyperkalemia has been observed in certain degree.[39] The progression from mild to severe hyperkalemia may not be predicted from EKG, which depends on a number of factors, including patient sensitivity and the acuteness of the development of hyperkalemia. Even though the progression from benign to fatal arrhythmias resulted from hyperkalemia is unpredictable, the presence of abnormal EKG findings should be considered as medical emergency. Besides these myocardial effects, hyperkalemia can also affect skeletal muscles and increase weakness and fatigue. Smooth muscles are also sensitive to elevated potassium level, which could result in severe respiratory depression.[83]

Even though hyperkalemia, defined as [K+] ≥ 6.3 mEq/L, occurs relatively frequently in inpatient settings, about 3.2% of all hospital admissions, deaths directly related to hyperkalemia are relatively rare.[84] It is considered life-threatening if serum potassium concentration reaches 6.5 mmol/L and /or cardiac signs appear.[85] Ponce et al. reported that hyperkalemia accounted for 1 out of 1000 deaths in hospitalized patients.[86] In another paper studied drug-associated

hyperkalemia in adult patients without end stage renal disease (ESRD), fatal outcomes, attributed to hyperkalemia, were observed for 9.8% of the patients with serum potassium concentration at least 6.5 mEq/L.[87]

2.3.3 Treatments

Treatment for hyperkalemia can be divided into three categories: minimizing the cardiac effects of hyperkalemia, shifting potassium into cells, and removing potassium from the body.

Blocking Cardiac Effects

Intravenous administration of calcium specifically antagonizes the effects of hyperkalemia on the myocardial conduction system and myocardial repolarization.[88] Being the most rapid way to treat hyperkalemia, intravenous calcium administration should be the initial treatment for patients with abnormal EKG related to hyperkalemia.

Cellular Potassium Uptake

The second effective way to treat hyperkalemia is to increase cellular uptake with insulin or β_2-adrenergic agonists. Unless the patient is already hyperglycemic, glucose is usually coadministered with insulin to avoid hypoglycemia, which can lead to further increase in potassium concentration due to hypertonicity-induced potassium redistribution. Albuterol is not approved for intravenous use in the U.S. because of its tachycardiac side effect.[89] It is often given by nebulizer, but may not be responsive in 20-33% of patients.[90, 91] Therefore, combined therapy with insulin and albuterol is often used for severe hyperkalemia.

Bicarbonate can also be used for hyperkalemia even though it is less effective than insulin or β_2-adrenergic agonists. It is reported that changes in serum potassium were insignificant and inconsistent with intravenous bicarbonate administration, and the sodium load from the drug may also worsen hypertension and contribute to the complication of acute

congestive heart failure.[92-94] Thus, sodium bicarbonate is not recommended for routine use in treating hyperkalemia.

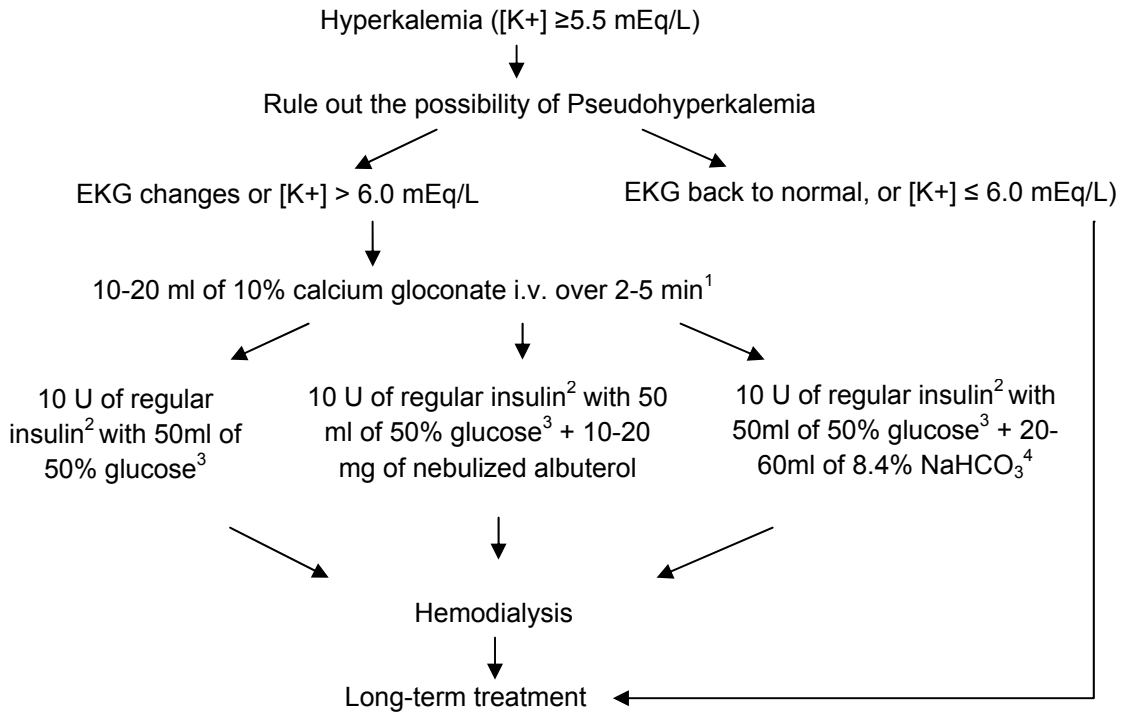
Potassium Removal

The definitive treatment for hyperkalemia is removal of potassium from the body. Loop or thiazide diuretics are usually used to accelerate renal potassium elimination, which may suffice in some conditions. However, most patients with hyperkalemia have underlying renal insufficiency as a contributing factor.[95] In that case, the effect of diuretics is limited, and sodium polystyrene sulfonate (SPS) is needed to eliminate potassium by exchanging sodium for potassium in gastrointestinal tract.[95]

Dialysis should also be considered as the primary method for potassium removal when renal function is impaired and persistent or severe hyperkalemia is developed.[39] Hemodialysis is the most rapid way to remove potassium; peritoneal dialysis, chronic arteriovenous hemodialysis, and chronic venovenous hemodialysis are used for chronic hyperkalemia, but are not recommended for acute severe hyperkalemia because of its slow speed in removing potassium.[39]

Besides these therapeutic approaches mentioned above, it is important to determine the underlying causes and pathophysiologic diagnosis for hyperkalemia in order to prevent reoccurrences for long-term treatment.[96] Dietary habit and medication use should be carefully examined. Laboratory tests such as arterial blood gas, urinary potassium concentrations, fractional excretion of potassium, and calculation of transtubular potassium gradient may be required to make the pathophysiologic diagnosis. The treatments protocol for severe hyperkalemia, which was defined as serum potassium concentration [K+] ≥5.5 mEq/L, were summarized by Kim et al.,[96] and illustrated below (Figure 2).

Figure 2 Flow chart for treatment of severe hyperkalemia[96]



[1]Can be repeated until resolving EKG changes; [2]intravenous bolus injection; [3]if blood glucose is more than 250mg/dl, can be omitted; [4]not proven unanimously.

2.4 Conceptual framework

2.4.1 Linking Laboratory and Pharmacy

Acknowledging the importance of linking laboratory and medication data in detecting and preventing medication errors related to laboratory parameters, Schiff and colleagues proposed ten ways that laboratory and pharmacy links can help to improve health care quality and enhance drug safety (TABLE I).[97] Communication between laboratory and pharmacy systems could help pharmacotherapy in drug choice, dosing, monitoring, laboratory interference and interpretation, and quality of care improvement. The authors stated that many health care

institutions could benefit from linked pharmacy and laboratory data, which can be done either retrospectively or in real time. They also argued that, when incorporated into synchronous CDS with electronic order entry, the linked pharmacy and laboratory data have great promise to improve the quality of care.

TABLE I TEN WAYS LAB AND PHARMACY CAN BE LINKED TO IMPROVE CARE[97]

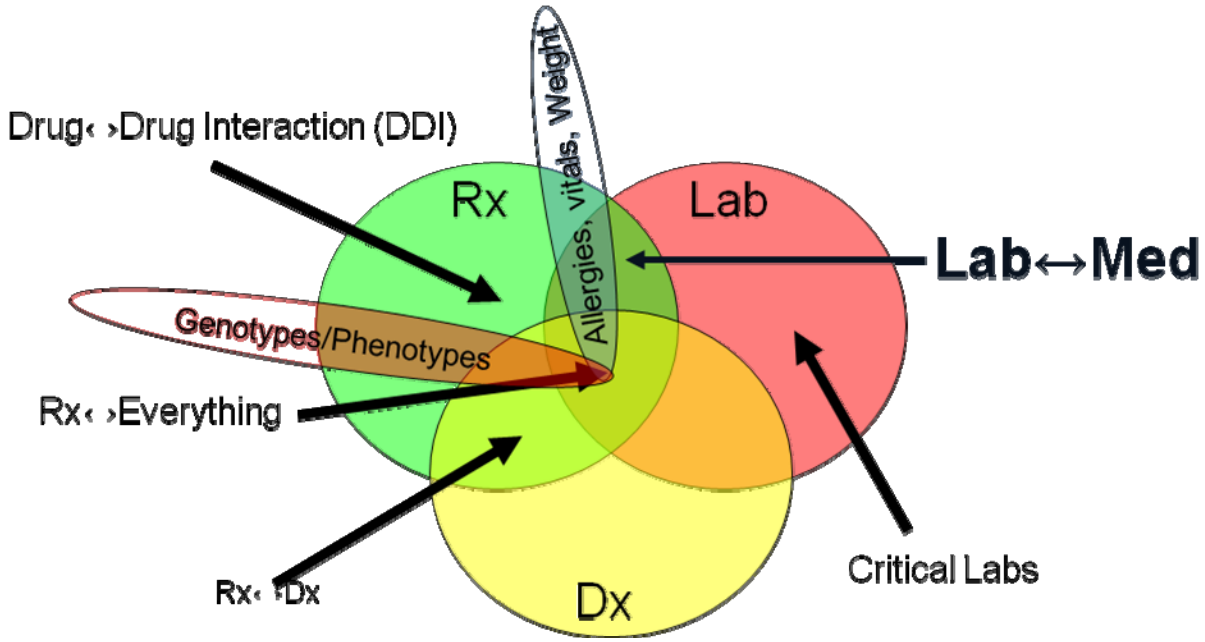
Category	Concept	Special roles for the linkages
Drug selection	1. Lab finding contraindicates drug	Prevents prescription writing or dispensing
	2. Lab finding suggests indication for drug	Generate timely reminders, tracking intervention
Dosing	3. Lab finding affecting drug dose	Performs dose calculations based on age, sex, lab value, weight
	4. Drug requiring lab measure for titration	Statistical process control dosing adjustment charts
Monitoring	5. Abnormal lab value signaling toxicity	Triggers alert, assesses likelihood
	6. Drug warranting lab value monitoring for toxicity	Oversees scheduling of both baseline and serial monitoring tests
Lab interpretation	7. Drug influencing or interfering with lab finding	Warms against/interprets false-positives and false-negatives
	8. Drug impacting on response to lab finding	Resets alarm threshold for treated patients
Improvement	9. Drug toxicity/effects surveillance	Data mining of lab and drug data to generate new hypotheses of drug effects
	10. Quality oversight	Monitors time interval between lab testing and prescription change, adequacy/appropriateness of lab monitoring

Note: This TABLE is adapted from Linking *Laboratory and Pharmacy: Opportunities for Reducing Errors and Improving Care* by Gordon D. Schiff, David Klass, Josh Peterson, Gaurav Shah, David W. Bates, published at Arch Intern Med 2003;163(8):893-900.

2.4.2 Laboratory and Pharmacy Linkage CDS

Galanter further depicted the targets for CDS to improve medication use (Figure 3).[98] He pointed out that optimal medication selection and dosing should not only be based on the diagnosis, but also be guided by the characteristics of individual patients, such as age, gender, allergies, vitals, weight, other medications, and critical biomedical parameters. These were the areas where CDSs could help to facilitate clinicians in providing better clinical care.

Figure 3 Targets for CDS to improve medication use



Abbreviations: Rx: medication; Dx: diagnosis.

After critical appraisal of the concurrent challenges associated with medication-related CDS, Kuperman et al. concluded that medication-related laboratory testing can be guided by advanced CDS, and it requires three prerequisites, including access to patients' previous

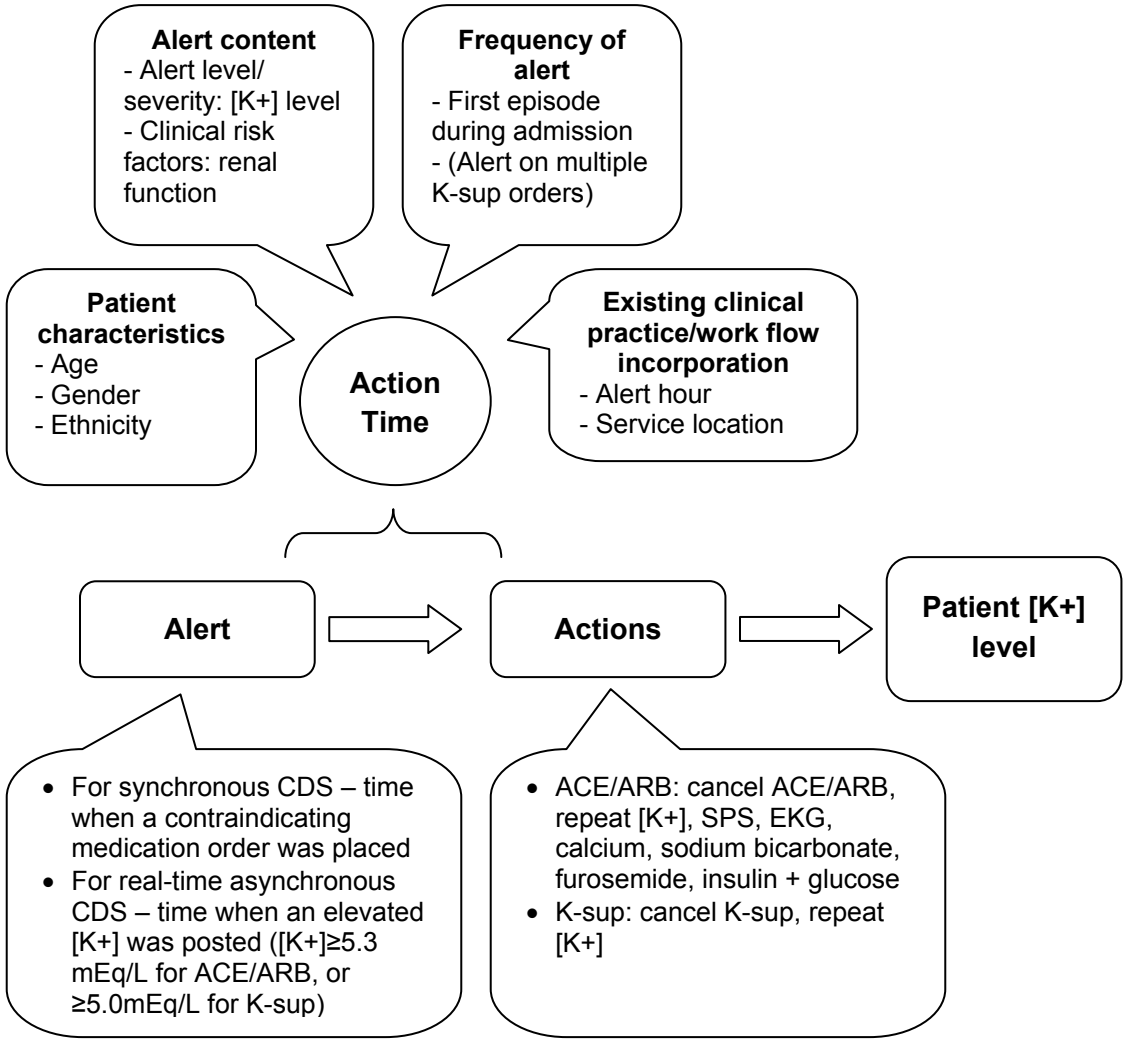
laboratory results, an alerting system to inform providers of needed laboratory tests, and evidence-base upon which the CDS guidance can be built.[20] They also recommended that systematic reviews and primary research should be conducted to establish the benefits of CDS-guided medication-related laboratory testing. When such evidence is not available or clear, consensus opinions from experts and accepted by clinicians can be used to determine monitoring intervals, but need to be updated regularly or whenever new evidence emerges. These recommendations echo the purpose of this study, and underscore its significance and necessity.

2.4.3 Analytical Framework

In light of the theoretical exploration of human factors principles and current findings from empirical research, this study chose action time as the measurement of clinicians' response. It was defined as the time that the alert was triggered until appropriate action was taken or previous hazardous condition was resolved. The previously identified factors that were associated with clinicians' responses and alert acceptance were further decomposed into four categories: 1) patient characteristics such as age, gender, and ethnicity; 2) alert content including alert level/severity and clinical risk factor; 3) alert frequency; and 4) work flow incorporation which means how well the alert intermingled with the existing clinical practice. Those four categories could intervene clinicians' decision making when responding to hyperkalemia, or influence alert ignorance and the system time when the alert would be responded.

Furthermore, the laboratory-pharmacy linkage CDS should also have an indirect effect on patient time to normal [K+] since the delayed action would probably result in longer time while patient was hyperkalemic.

Figure 4 Analytical framework of the study



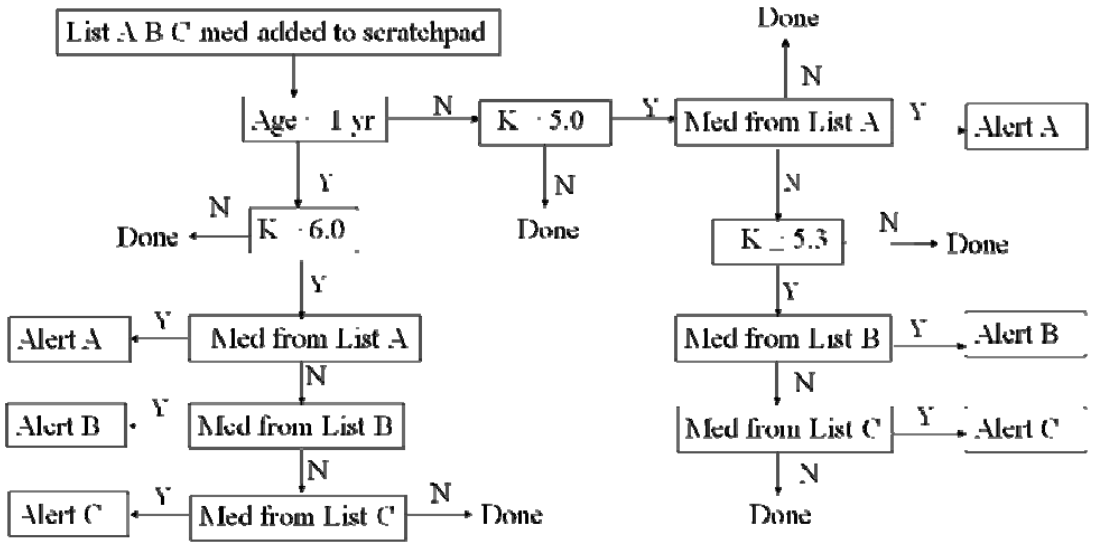
3. METHODS

3.1 Health Information Technology Environment at UIMC

In August 1999, an EHR (Millennium®, Cerner Corporation, Kansas City, MO) was deployed at UIH, a 450-bed urban teaching hospital in a major academic health center.[27] It has been used as the primary storage for results, problem lists, clinical notes, medication lists, and orders. All physician users were mandated to use EHR for documenting patient care and retrieval of laboratory and radiological information.[31] During November of the same year, CPOE was implemented on all UIH inpatient units. From then on, all inpatient medication orders have been placed using CPOE. Afterwards, a commercially available CDS system (Discern Expert, Cerner) was gradually built up to alert contraindicated medication use,[29] link laboratory results with medication use,[30] prevent exacerbation of ADEs,[28] and assist clinical risk assessment.[99]

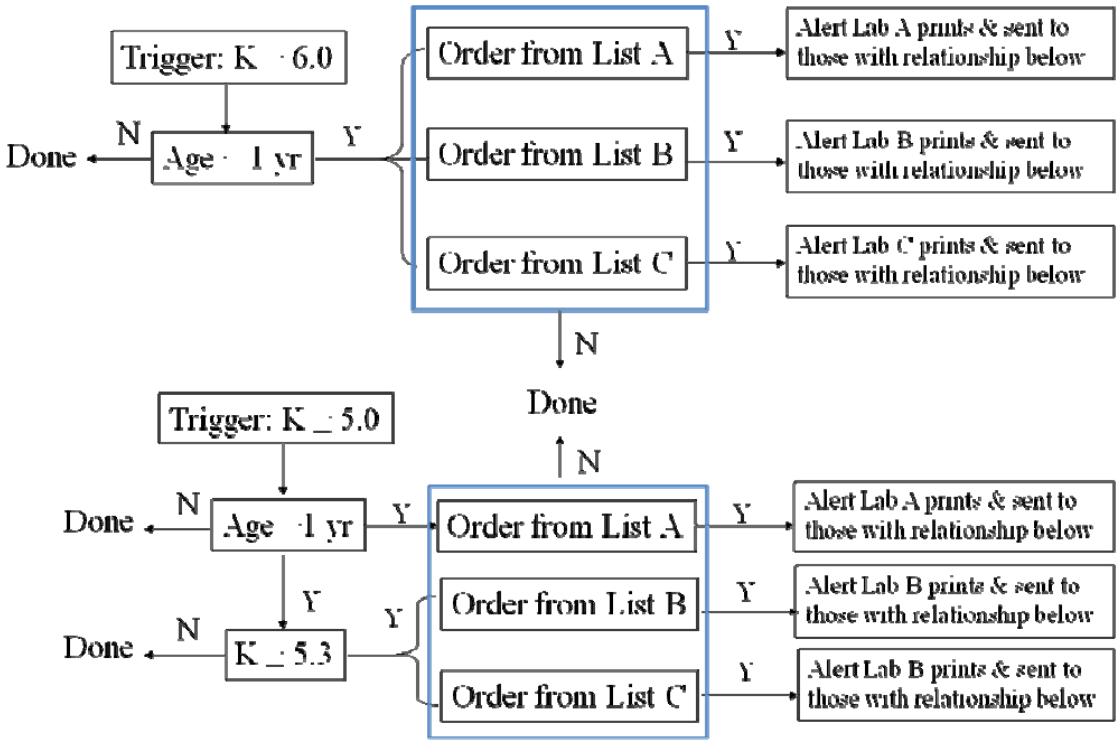
Among those CDS interventions, the CDS alerts for elevated [K+] for patients on ACE inhibitors, ARBs, and K-sup were implemented in June 2003 (Figure 5, 6). The CDS system could be evoked on two conditions: 1) ordering a medication from List A, B, and C, when [K+] > 6.0 mEq/L for patients under 1 year or [K+] ≥ 5.0 mEq/L (K-sup) or ≥ 5.3 mEq/L (ACE/ARB) for patients aged 1 year and older; 2) when an elevated [K+] test result came back and the patients had an active order for any of the medication from List A, B, and C. In the first situation, the scripted warning message would be displayed on the order entry screen with patient name, the most recent [K+] result, and the name of the medication being ordered. In the second situation, printout with the same script message would be sent to designated nursing stations and inpatient pharmacies, and to the electronic clinical inbox of the on-call physicians.

Figure 5 Synchronous CDS alert for elevated potassium level[100]



List A	K-Dur, Klor-Con, Micro-K, KCl, K-Phos
List B	Angiotensin-converting-enzyme, Angiotensin II receptor Blockers, Lotrel, Lexxal, Tarka
List C	amiloride, amiloride-HCTZ, midamor, moduretic, aldactazide, spironolactone, Aldactone, Dyazide, triamterene, Inspra
Alert A	*You are ordering [List A] for the patient [name], whose most recent serum potassium level was [result]. Because potassium supplementation may worsen this condition, consider discontinuing this order until this patient's hyperkalemia has resolved.*
Alert B	*You are ordering [List B] for the patient [name], whose most recent serum potassium level was [result]. Because ACE inhibitors & ARBs may worsen this condition, consider discontinuing this order until this patient's hyperkalemia has resolved.*
Alert C	*You are ordering [List C] for the patient [name], whose most recent serum potassium level was [result]. Because potassium-sparing diuretics may worsen this condition, consider discontinuing this order until this patient's hyperkalemia has resolved.*

Figure 6 Real-time asynchronous CDS alert for elevated potassium level[101]



List A	Potassium supplements
List B	Lisinopril, captopril, enalapril, losartan
List C	amiloride, amiloride-HCTZ, spironolactone, triamterene, epleronone
Alert Lab A	*Patient [name] has a high serum potassium level of [result] and has an existing order for [List A]. Because potassium supplementation may cause or worsen hyperkalemia, please consider discontinuing [List A med].*
Alert Lab B	*Patient [name] has a high serum potassium level of [result] and has an existing order for [List B]. Because ACE inhibitors & ARBs may cause or worsen hyperkalemia, please consider discontinuing [List B med].*
Alert Lab C	*Patient [name] has a high serum potassium level of [result] and has an existing order for [List C]. Because potassium-sparing diuretics may cause or worsen hyperkalemia, please consider discontinuing [List C med].*

In May 2010, another daily report for a series of lab↔drug pairs was implemented in addition to the existing two alerts.[102] Using real-time information obtained from the EMR, this report sought to identify patients whose linked lab and pharmacy data suggested the need for

clinical intervention to address a potentially dangerous situation. The report runs once a day at the pre-set time of the day. The alert is triggered at the presence of an active order for a target medication with the most recent target laboratory test result within the predefined alerting range. A report is generated after combining all the triggered alerts. Patient name, medical record number, lab↔drug pair, weight, service location, triggering medication and its dose and frequency, medication ordering date and time, and laboratory test ordering date and time and its value, are included with each alert. The report is then delivered automatically to a secure hospital intranet directory, and the responsible clinicians will be contacted to address the identified problem. The three pairs that being studied, [K+]↔ACE inhibitor, [K+]↔ARBs, and [K+]↔K-sup, were implemented during the first phase. Ten months of data were available for assessing how well these retrospective linkages can help in detecting potentially harmful problems in a more timely fashion.

Based on the definition in the published literature and common use of those terms, the alert that was triggered at the medication order entry was referred as the synchronous CDS alert, and the other two alerts as asynchronous. In order to distinguish the two asynchronous alerts, the alert triggered by the posting of elevated [K+] was referred as the real-time asynchronous alert as it was real-time at the posting of lab results. And the other retrospective asynchronous alert was referred as once daily report in the following text.

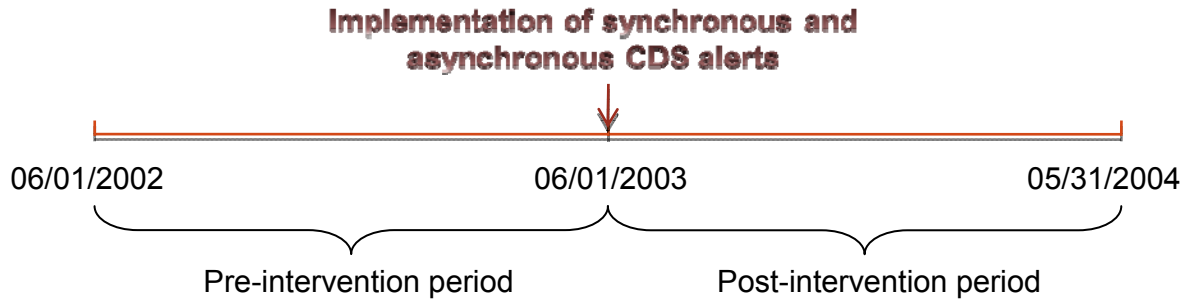
3.2 Evaluation of Synchronous and Real-time Asynchronous CDS alert

3.2.1 Study Design, Study Sample, and Data Source

The assessment of synchronous and real-time asynchronous CDS alert was conducted through a retrospective analysis of EHR data collected from regular clinical care encounters (Figure 7). Potassium test and medication use data for all patients on ACE inhibitors (benazepril,

captopril, enalapril, and lisinopril), ARB (only losartan at the time), or K-sup from June 1st, 2002 to May 31st, 2004 were pulled from the UIH medication and laboratory database through programmed computer queries. Since different laboratory thresholds were used for neonatal and infant patients (i.e. age < 1 year) and those patients had higher potassium tolerance, only patients aged 1 year and older were selected as the study sample. Different [K+] thresholds were applied for the ACE/ ARB and K-sup sample. ACE/ARB users had to have at least one laboratory potassium test, during the study time frame, with a result that was ≥ 5.3 mEq/L in order to be included in the study sample, while the laboratory cutoff was ≥ 5.0 mEq/L for K-sup users.

Figure 7 Study period for assessment of synchronous and real-time asynchronous CDS alerts



Additionally, patients who had ESRD were excluded from the ACE/ARB sample, but not the K-sup sample. ESRD patients were more likely to have higher [K+] due to their impaired renal function. For ACE/ARB users with ESRD, the appropriate clinical action for hyperkalemia would be dialysis. However, ESRD is irrelevant in managing hyperkalemia for K-sup users. Thus, patients with ESRD were included in the K-sup study. ESRD patients going through hemodialysis or peritoneal dialysis were identified by reviewing nephrology consult orders

during the medical chart review process. Since dialysate solutions usually contain a certain amount of potassium, dialysis orders were excluded from the medication orders under study.

3.2.2 Data Management

The EHR was queried based on the inclusion criteria specified above. Separate data files were constructed for patient demographics, medication orders, laboratory data, and nephrology consult orders. The patient identifier, FIN number, was saved in each file in order to link those different pieces of information and merge those files for medical chart review and statistical analysis. Data was then imported into SAS version 9.1.3 (SAS Institute, Cary, NC, USA) for data cleaning. Afterwards, a summary table with patient FIN number, laboratory tests, medication orders, and nephrology consult information was constructed in Excel (Microsoft Excel 2007, Redmond, WA, USA) to facilitate medical chart review. All statistical analyses were performed using SAS. Result figures were created using either Stata SE 10.0 (StataCorp LP, College Station, TX) or Excel 2007.

Data containing personal health information was stored in a password-protected computer located in a locked office that only the investigator and her advisors had access to. This study was reviewed and approved by the Institutional Review Board at University of Illinois at Chicago under the protocol number 2009-0429. The conduct of this study was fully compliant with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

3.2.3 Medical Chart Review

A medical resident and a 4th year medical school student helped to conduct the medical chart reviews to determine the eligibility of study subjects and evaluate clinical actions that were relevant to managing hyperkalemia for ACE/ARB users.

As part of another related study, the repertoire of clinical actions treating hyperkalemia for patients taking ACE inhibitor and ARB had been built based on the clinical recommendations, clinical expertise, and the findings from the chart review of a small random sample of the study subject. The possible clinical actions were summarized as follows:

- Cancel the ACE inhibitor or ARB
- Add a diuretic (furosemide)
- Repeat potassium test
- Administer SPS
- Administer albuterol
- Administer calcium gloconate
- Administer insulin and glucose
- Order EKG

After confirming the non-ESRD status of the patients, reviewers examined the medical charts and clinical notes thoroughly to determine whether these actions, if available, were taken for the purpose of addressing hyperkalemia. All the possible actions were evaluated separately, and the time to the first action was used to assess the effect of CDS alerts in improving clinicians' responses.

Hemolysis occurs frequently to blood samples, which results in "pseudohyperkalemia" due to the potassium released from blood cells.[39] When the serum is hemolyzed, potassium tests need to be redone in order to get an accurate measure of serum potassium level. Therefore, hemolyzed samples were treated as non-hemolyzed ones in chart review, since the proper action after receiving a hemolyzed sample for a patient who was at risk for hyperkalemia was to repeat the test, which was also one of the expected actions for treating hyperkalemia for ACE/ARB users.

In comparison to the clinical responses to hyperkalemia related to ACE inhibitor and ARB use, actions to treat hyperkalemia in patients taking K-sup were more straightforward. Besides other actions for addressing hyperkalemia, canceling the K-sup order and/or repeating [K+] were always expected to be the first actions. Thus, no chart review was conducted, and the time to first action was measured from the alert time to the time of canceling K-sup or repeating [K+].

3.2.4 Statistical Analysis

3.2.4.1 Outcome measurement

The primary purpose of this study was to assess the effect of synchronous and real-time asynchronous CDS alerts on clinicians' action in managing inpatient hyperkalemia (Objective 1). In order to achieve this objective, the effect of two CDS alerts was evaluated separately for both [K+]↔ACE/ARB and [K+]↔K-sup, and the combined effect of both alerts was assessed for the [K+]↔K-sup only.

The effect of synchronous CDS

The effect of synchronous CDS alert was measured by the clinicians' compliance with the synchronous alert, or in another words, the order cancellation rate after CDS implementation. Technically, order cancellation or clinicians' compliance was defined as no medication order being placed within one hour of the relevant alert. The synchronous alert was also expected to have an indirect effect on the alert rate of the real-time asynchronous alert. Therefore, the alert rate of asynchronous alerts during the post-intervention period was compared with the rate of potential asynchronous alert during the pre-intervention period. Since there was no real-time asynchronous alert in place before June 2003, [K+] above the defined threshold that were posted while the relevant medication order was active were treated as potential real-time asynchronous alerts for the pre-intervention period.

The effect of real-time asynchronous CDS

The effect of the real-time asynchronous alert was measured by two outcomes: time to the first action (clinicians' action time), and patient time to normal [K+]. The action time was calculated from the posting time of the elevated [K+] till the time performing any of the actions identified from the chart review for [K+]↔ACE/ARB and cancelling the K-sup order or repeating [K+] for [K+]↔K-sup. During each admission which was identified by the FIN number, an elevated [K+] after [K+] went under the alerting range was considered as a separate hyperkalemic episode. The time to normal [K+] was defined as the time between the posting time of the elevated [K+] until the time when the serum sample of the next available normal [K+] was drawn.

The combined effect of both CDS alerts

Both the synchronous and the real-time asynchronous alerts were expected to reduce the use of medication in the hazardous conditions as alerted by CDS alerts. Since cancelling K-sup order was one of first expected actions in response to hyperkalemia, any decrease in the patient time on K-sup would be the combined effect of both CDS alerts. Therefore, total patient time on K-sup normalized by total patient admission days during the same period and also the patient time on K-sup while [K+] ≥ 5.0 mEq/L normalized by total patient time on K-sup were used to measure the combined effect of both alerts. Because cancelling ACE inhibitor or ARB was not always necessary when hyperkalemia occurs, patient time on ACE inhibitor or ARB was not a valid outcome to measure the combined effect of CDS alerts.

3.2.4.2 Independent variables

As described in the analytical framework, the time until appropriate action was influenced by patient characteristics, alert content, alert frequency, and work flow incorporation. Independent variables were deliberately chosen to address those four categories. Patient age, gender, and ethnicity were included to describe patient characteristics; [K+] level and creatinine

clearance level were the ones that represented the alert severity and clinical risk factor; whether being the first hyperkalemic episode during the admission and being alerted on multiple K-sup orders were the indicators for alert frequency; and the hour of the day when alert was fired and the service location of the patient were variables representing factors that affect work flow incorporation.

In the descriptive analysis, age was treated as a continuous variable. Patient subjects were further classified according to whether they were age 1-19, 20-44, 45-64, or ≥ 65 years of age for regression analysis. The race and ethnicity information collected by the EHR system of UIH was not mandatory and thus incomplete. Given the limited race information, patients were categorized as Non-Hispanic, Hispanic, and Unknown.

Hyperkalemia was defined using different thresholds in published literature, ranging from 5.0 mEq/L to 6.3 mEq/L.[4, 41, 85, 87] Despite the lack of evidence about the association of myocardial events and severity of hyperkalemia, [K+] level was grouped based on the cutoffs used by the UIH laboratory and the alert threshold of the synchronous and asynchronous CDS alerts. As described previously, [K+] ≥ 5.0 mEq/L for [K+]↔K-sup and ≥ 5.3 mEq/L for [K+]↔ACE/ARB would trigger the CDS alerts. At UIH, [K+] between 5.0-5.3 mEq/L was considered as normal high, while [K+] above 6.1 mEq/L was considered critical that required immediate contact with the patient care unit via the critical value reporting mechanism.[48] Thus, [K+] level was categorized as 5.3-5.6 mEq/L, 5.7-6.0 mEq/L, and ≥ 6.1 mEq/L for [K+]↔ACE/ARB, and 5.0-5.3 mEq/L, 5.4-6.0 mEq/L, and ≥ 6.1 mEq/L for [K+]↔K-sup.

Even though the estimated glomerular filtration rate is more accurate in indicating renal function, only creatinine clearance (CrCl) level was available during the study period.[103] The estimated CrCl is based on the measured serum creatinine and calculated using Cockcroft and Gault formula.[104] At UIH, the normal range of CrCl for adult males is greater than 95 mL/min, and great than 85 mL/min for adult females. CrCl level less than 25 mL/min presents the need

for routine dialysis. Therefore, creatinine clearance level was categorized into normal (>95 mL/min for male, and >85 mL/min for female), impaired (95/85-26 mL/min), and severe (≤ 25 mL/L).

Since the intensive care unit (ICU) has higher nurse/physician-to-patient ratio than general medical and surgical units, service location was classified as medical/surgical unit and ICU. The normal day shift at UIH starts at 7am and ends at 5pm. Thus, time of the day when alert was fired was categorized as midnight - <7am, 7am - <5pm, and 5pm - <midnight. Those above mentioned categorization were used for both descriptive statistics and regression modeling.

TABLE II LIST OF INDEPENDENT VARIABLES

Variable	Categories
Patient characteristics	
Age	1-19
	20-44 (referent)
	45-64
	≥ 65
Gender	Male (referent)
	Female
Race/ethnicity	Non-Hispanic (referent)
	Hispanic
	Unknown
Alert content	
[K+] level	ACE inhibitor and ARB
	5.3-5.6 mEq/L (referent)
	5.7-6.0 mEq/L
	≥ 6.1 mEq/L
	Potassium supplementation
	5.0-5.3 mEq/L (referent)
	5.4-6.0 mEq/L
	≥ 6.1 mEq/L
Creatinine clearance	Normal: > 85 for female, > 95 for male
	Impaired: 85/95-26 (referent)
	Severe: ≤ 25
Alert frequency	
First episode during admission	Yes (referent)
	No
Alerted on multiple K-sup orders	Yes (referent)
(for [K+]↔K-sup only)	No
Work flow incorporation	
Service location	Medical/surgical unit (referent)
	Intensive care unit
Posting time of [K+]	Midnight - <7am
	7am - <5pm (referent)
	5pm - <midnight

3.2.4.3 Descriptive Statistics

Descriptive statistics were reported for all outcome variables and independent variables both at the patient level and also at the episode level. The unit of analysis for this study was the hyperkalemic episode. Patients could have multiple admissions, and each admission could have multiple hyperkalemic episodes. Since K-sup orders were usually placed at the same time, one single elevated [K+] could have alerted on multiple orders. In this case, those alerts, even though they were actually one "alert", were considered as separate alerts.

The order cancellation rate for synchronous CDS alerts was calculated at monthly intervals for the post-intervention period, and only based on the orders placed on patients aged 1 year and older. The alert rate of the real-time asynchronous alerts for the post-intervention was calculated and compared with that for the pre-intervention period in order to demonstrate any indirect effect of synchronous CDS alert.

Due to the possibility of insufficient sample size and the similarity of clinical actions, ACE inhibitor and ARB samples were combined and analyzed together in both descriptive analysis and regression analysis in order to achieve more statistical power. The results were reported for [K+]↔ACE/ARB and [K+]↔K-sup separately. Estimated means and standard errors were reported for continuous variables, while calculated percentages and observed cell counts were reported for categorical variables. F tests for categorical variables and 1-way ANOVA test for continuous variables were performed to examine any change in the patient population between the pre-intervention and post-intervention period.

3.2.4.4 Survival Analysis of Action Time and Time to Normal [K+]

Time to the first action and patient time to normal [K+] during the pre-intervention and post-intervention period were plotted using the Kaplan-Meier method, and log-rank test was performed to test for difference before and after CDS implementation. The action time was censored at the posting time of the next available normal [K+], patient discharge, death, or 48

hours after alert time, whichever occurred earlier. Patient time to normal [K+] was censored at patient discharge, death, or 5 days after the alert time, whichever occurred earlier.

Cox proportional hazards models were used to examine the effect of the covariates on clinicians' action time in response to hyperkalemia and patient time to normal [K+] (Objective 2). Besides the indicator variable for CDS intervention, patient age, gender, ethnicity, [K+] level, CrCl level, whether being the first episode of the admission, time of the alert, and service location were included as the covariates. For [K+]↔K-sup, whether the alert was fired on multiple K-sup orders was also included as one of the covariates. The coefficient estimate, standard error, hazard ratio (HR), and associated p-value were reported for each independent variable except for the referent categories. Given the context of action time as the outcome of the survival analysis, HR greater than 1 indicates shorter action time for the associated category as compared to the referent category. P-value less than 0.05 was used to assess the statistical significance of the impact of those factors.

3.2.4.5 Segmented Regression Analysis

Even if significant difference was observed in action time and/or patient time to normal [K+] in the Survival Analysis, no conclusion could be made regarding the effect of CDS alerts in reducing clinicians' action time and patient time to normal [K+]. This was because the difference could result from secular changes in care patterns that were not related to the CDS implementation. Therefore, segmented regression analysis was conducted to answer the question whether laboratory-pharmacy CDS helped to improve the clinicians' practice behavior and patient outcome (Objective 1). In order to adjust for all the covariates, the individual episode level data, rather than integrated monthly data, was used for the regression model. The basic model construction was illustrated as follows:

Action time / Time to normal [K+]

$= \beta_0 + \beta_1 \times time_t + \beta_2 \times intervention_t$

$+ \beta_3 \times$time after intervention$_t$ + (covariates) + e_t

where *time*$_t$ is the variable indicating time in months from the start of the observation period, and *time after intervention*$_t$ is the indicator counting the number of months after intervention which occurred at time *t*. The *intervention*$_t$ is a binary variable indicating whether *time*$_t$ occurred before intervention or after. In this study, both the synchronous and asynchronous CDS alerts were implemented at the beginning of June 2003, which is the 13th month from the start of observation period. Thus, for month 1 to month 12, intervention$_t$ = 0 and time after intervention$_t$ = 0; for month 13 to month 24, intervention$_t$ = 1 and time after intervention$_t$ = time$_t$ - 12.

In this model, β_0 is the parameter estimates the baseline level of the outcomes, which is the median time to first action or total patient-days on potassium per 1000 non-obstetric hospitalized patient-days at time 0. β_1 estimates the monthly change in the outcomes before alert implementation; while β_3 estimates the additional monthly change, beyond the pre-intervention trend estimated by β_1, after alert implementation. The sum of β_1 and β_0 is the estimate for the monthly change after intervention. β_2 estimates the immediate change in the outcomes that occurred right after the intervention. Therefore, the hypothesis of whether laboratory-pharmacy linkage CDS reduced clinicians' action time or patient time to normal [K+] can be tested alternatively as H_0: $\beta_2 < 0$ and/or $\beta_3 < 0$.

As described earlier in this section, clinicians' practice behavior could change over the time period, whether due to the impact of laboratory-pharmacy linkage CDS or not. Thus, the Durbin-Watson statistic was used to assess the serial autocorrelation of the error terms, e_t. Values close to 2.00 indicate no serious autocorrelation existed.[105] The first order autoregressive error structure, AR(1), was used to fit the segmented regression model if Durbin-Watson statistics was not close to 2.00 and AR(1) coefficient estimate was significant.

In order to evaluate the combined effect of synchronous and real-time asynchronous alerts for [K+]↔K-sup, the monthly time series of total patient time on K-sup per admission day

and the patient time on K-sup while [K+] ≥ 5.0 mEq/L per K-sup day were also modeled using segmented regression. It is recommended that 12 time points before and after the intervention with at least 100 observations at each time point were sufficient to evaluate seasonal variation and achieve acceptable variability of estimate at each time point.[106] The pre-intervention data from June 2002 to May 2003 and the post-intervention data from June 2003 to May 2004 were grouped by monthly intervals. These two integrated outcomes were analyzed by two segmented regression models separately, and both models were regressed on intervention indicator, and two time indicators.

The outlines of the outcome measurement and statistical methods used for each outcome were summarized in TABLE III.

TABLE III OUTLINES OF OUTCOME MEASUREMENT

	Outcomes	Statistical methods
Effect of synchronous CDS	• Cancellation rate after implementation • Alert rate of asynchronous CDS	Descriptive statistics Chi-square test of association
Effect of real-time asynchronous CDS	• Clinicians' action time • Patient time to normal [K+]	Survival curves using Kaplan-Meier method, and Log-rank test Cox proportional hazards regression Segmented regression using episode level data
The combined effect of both synchronous and real-time asynchronous CDS, and the effect of the once daily report (for [K+]↔K-sup only)	• Patient time on K-sup, normalized by total patient admission days • Patient time on K-sup while [K+] ≥ 5.0 mEq/L, normalized by total patient time on K-sup	Segmented regression using integrated monthly data

3.2.4.6 Model Selection

Due to the missing information for patient race/ethnicity information, the regression model was run both with and without the ethnicity variables. If neither of the ethnicity variables was significant in the full model (i.e. the model with ethnicity variables), Log-likelihood ratio test was performed to determine the necessity of including ethnicity variables.

Additionally, Durbin-Watson statistics was used to test the degree of autocorrelation for the segmented regression models. Durbin-Watson statistics value not close to 2.00 and the significance of the autocorrelation coefficient estimate were the two criteria that were used for keeping the autocorrelation coefficient. When there was no need to adjust for autocorrelation, ordinary least squares estimates was used for the regression model, and partial F-test was used to determine the necessity of including ethnicity variables.

3.3 Development of Daily Laboratory-pharmacy Report

3.3.1 Logic Building

The daily laboratory-pharmacy report was built for the purpose of identifying patients whose linked lab and pharmacy data suggest the need for clinical intervention that was not addressed by the real-time asynchronous CDS alert. As part of another related study, the alerting range for the once daily report was determined based on the frequency distributions of the laboratory results, FDA labeling, if available, and clinical expertise in order to achieve the maximized signal-to-noise ratio without producing alert fatigue. Medication order and laboratory test data from January 1, 2009 to June 14th, 2009 was used to simulate the alert assuming [K+] cutoff from 5.0 mEq/L to 6.5 mEq/L at the interval of 0.1 mEq/L. The distribution of the hypothetical alert count by different [K+] level was used to determined separate optimal cutoffs for [K+]↔ACE inhibitor, [K+]↔ARBs, and [K+]↔K-sup. The potential optimal cutoffs should be above the thresholds that have been used by the real-time asynchronous CDS alert and should produce less than 3 alerts per day for a 450-bed hospital, which was considered as a manageable workload for the clinical safety team.

The best time of the day to run the report was chosen based on the simulated time analysis of the total patient time in danger. The total patient time in danger was calculated

assuming the potentially dangerous situation, which was defined by having [K+] above the defined cutoff, would be resolved in two hours from the time when the report was run. Thus, patient time in danger starts from the initial presence of dangerous [K+], the posting time, until two hours after the report time under testing. According to the assumption, the potassium tests posted before the report on the same day would be captured by the report and be addressed within two hours. However, those tests posted after the daily report was run would not be addressed until the report time the following day, if the clinicians had not already responded to the real-time asynchronous alert. The posting time of the laboratory tests usually depends on the workflow and practice pattern at individual institution, and is usually quite consistent over the time. In that case, the sum of patient time in danger for all cases would depend on the time of the day when the report was run. Therefore, the best report time could be identified when the total patient time in danger was minimized. When implementing the once daily report, this selected time based on the simulated time analysis might be modified to a less than optimal time in order to batch the reports or for the clinical safety team to be in the position to receive the data, but was still be reported for the demonstration purpose.

After the optimal laboratory cutoffs and best report time of the day were decided for each pair, report logic was built into the UIMC's EHR system and approved by the hospital's information services.

3.3.2 Evaluation of the Daily Laboratory-pharmacy Report

Since May 2010, the once daily report has been running at UIH at the designated time of the day. The reports were reviewed and saved manually, and the corresponding clinicians were contacted by the report reviewer if clinical intervention was needed. Begining June 28th 2011, additional programming was done to automatically pull the report alerts and save them on the

hospital server. Although the once daily report data was available since May 2010, only the alerts from June 28th 2011 to October 3rd 2011 were accessible at the time of this study.

The retrospective and asynchronous nature of the once daily report limited its potential effect only on clinicians' action time, patient time to normal [K+], and patient time on K-sup. Therefore, the segmented regression analysis of the above mentioned three outcomes were performed to evaluate the effect of the once daily laboratory-pharmacy report (Objective 4). The same statistical analyses as described for the 2003 intervention were repeated using the data from May 2009 to April 2010 (pre-intervention) and from May 2010 to April 2011 (post-intervention). The same inclusion and exclusion criteria were applied to select the study sample. Since the study for [K+]↔ACE/ARB requires additional chart review to determine whether certain action was taken in addressing hyperkalemia, the evaluation of once daily report was focused on [K+]↔K-sup.

4. RESULTS

4.1 [K+]↔ACE/ARB

4.1.1 Patient characteristics and Descriptive Statistics

After applying the inclusion and exclusion criteria, 432 patient admissions that had or would potentially have the real-time asynchronous alert were identified during the 2-year study period from June 2002 to May 2004. The mean age was 59.49 years for the pre-intervention study sample, and 60.93 years for the post-intervention sample. The majority of the patients were 45 years and older (85.8% for pre-intervention period and 86.0% for the post-intervention period). Race and ethnicity information was missing on 67.6% of the pre-intervention admission and 62.3% of the post-intervention admission. In general, the pre- and post-intervention study samples had similar demographic characteristics in terms of age, gender, and ethnicity since the difference was not statistically significant.

TABLE IV ACE/ARB PATIENT CHARACTERISTICS
FOR REAL-TIME ASYNCHRONOUS ALERTS[a]

	Pre-intervention (n = 225)	Post-intervention (n = 207)	p-value
Age (year), mean [s.e.]	59.49 [17.46]	60.93 [16.75]	0.383
1-19	4.0% (9)	1.9% (4)	0.586[b]
20-44	10.2% (23)	12.1% (25)	
45-64	42.7% (96)	44.0% (91)	
≥65	43.1% (97)	42.0% (87)	
Male	42.2% (95)	45.4% (94)	0.505
Ethnicity			
Non-Hispanic	27.1% (61)	27.1% (56)	0.117
Hispanic	5.3% (12)	10.6% (22)	
Unknown	67.6% (152)	62.3% (129)	

[a] The distribution of the categorical variables was reported in percentages, while the corresponding sample size was shown in brackets.
[b] Fisher's exact test was performed to obtain the p-value.

There were 236 potential real-time asynchronous alerts that would have fired during the pre-intervention period, and 215 real asynchronous alerts actually fired during the post-intervention period. Among those alerts, 69.1% of the pre-intervention alerts and 68.4% of the post-intervention alerts were posted during the day shift from 7am to 5pm. There were 52.1% of the pre-intervention alerts and 55.3% of the post-intervention alerts with [K+] level of 5.3-5.7 mEq/L, while 24.2% of the pre-intervention alerts and 21.4% of the post-intervention alerts were on or above the critical reporting value of 6.1 mEq/L. Most of the alerts fired on patients with some level of renal function insufficiency. Even after excluding the ESRD patients, 16.4% of the pre-intervention alerts and 15.2% of the post-intervention alerts fired on patients with CrCl level equal or less than 25 mL/min. Over 95% of the alerts were the first hyperkalemic episode of the admission, and 79.7% of the pre-intervention alerts and 75.4% of the post-intervention alert were from general medical or surgical units.

Among the eight possible actions in response to hyperkalemia among ACE/ARB users, clinicians were most likely to repeat [K+] as the first action (36.4% and 40.9% for pre- and post-intervention period), followed by administrating SPS (29.7% and 24.2% for pre- and post-intervention period) and canceling ACE/ARB (3.8% and 6.5% for pre- and post-intervention period). Other expected actions like ordering EKG, giving calcium, sodium bicarbonate, furosemide, and insulin were also observed but much less frequently. However, quite a few hyperkalemic cases, 27.1% during pre-intervention and 23.7% during post-intervention, were left untreated until the patient was discharged or [K+] came back under the threshold eventually. For those cases that medical actions were taken, the mean action time was 3.81 hours and 3.79 hours after alert time for pre-intervention and post-interventional periods, respectively ($p = 0.967$). Among the 81.4% of the pre-intervention alerts and the 83.3% of the post-intervention alerts, [K+] went down under the alert threshold of 5.3 mEq/L before discharge, after an average time period of 53.59 hours and 17.44 hours before and after CDS implementation.

Those factors, such as time of the alert, renal function, being the first hyperkalemic episode during the admission, service location, clinicians' action time, and time to normal [K+], did not differ between the pre- and post-intervention groups. However, the first action in response to hyperkalemia changed after CDS implementation.

TABLE V DESCRIPTIVE STATISTICS FOR REAL-TIME ASYNCHRNOUS [K+]↔ACE/ARB ALERTS

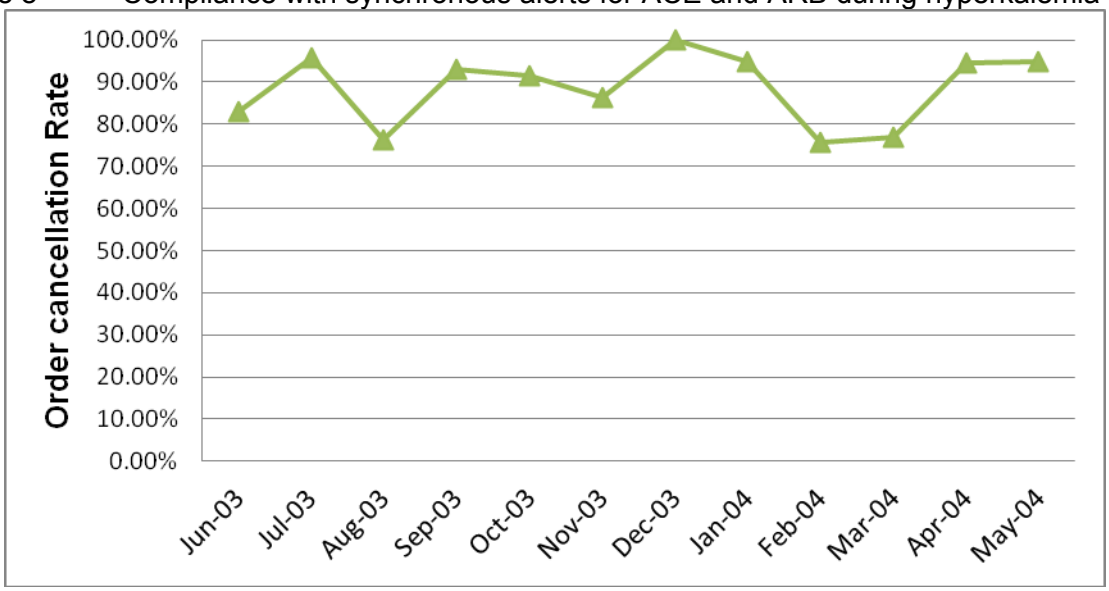
Variables	Pre-intervention n = 236	Post-intervention n = 215	P-value
Time of the alert			0.224
Midnight - <7am	22.0% (52)	18.1% (39)	
7am - <5pm	69.1% (163)	68.4% (147)	
5pm - <Midnight	8.9% (21)	13.5% (29)	
[K+] level			0.739
5.3-5.6	52.1% (123)	55.3% (119)	
5.7-6.0	23.7% (56)	23.3% (50)	
6.1 and above	24.2% (57)	21.4% (46)	
Creatinine clearance (eGFR not available at this time)			0.414
>85 for female, >95 for male	9.7% (22)	13.8% (29)	
85/95 - 26	73.9% (167)	71.0% (149)	
≤25	16.4% (37)	15.2% (32)	
First episode	95.3% (225)	96.3% (207)	0.620
Service location			0.273
Medical/surgical	79.7% (188)	75.4% (162)	
ICU	20.3% (48)	24.7% (53)	
First Action			0.029[a]
Repeat [K+]	36.4% (86)	40.9% (88)	
SPS	29.7% (70)	24.2% (52)	
Cancel ACE/ARB	3.8% (9)	6.5% (14)	
EKG	0.0% (0)	3.3% (7)	
Calcium	1.3% (3)	0.0% (0)	
Sodium bicarbonate	0.8% (2)	0.5% (1)	
Furosemide	0.4% (1)	0.5% (1)	
Insulin + glucose	0.4% (1)	0.5% (1)	
Action time (hour), mean [s.e.]	3.81 [4.39]	3.79 [22.39]	0.967[b]
Censored cases	27.1% (64)	23.7% (51)	0.408
Time to normal [K+] (hour), mean [s.e.]	53.59 [426.5]	17.44 [19.61]	0.242
Missing time to normal [K+]	18.6% (44)	16.7% (36)	0.598

[a] Monte Carlo estimation of exact p-value for the Fisher's exact test
[b] Calculated based on uncensored cases

4.1.2 Effect of Synchronous CDS Alert

The monthly order cancellation rate in response to the synchronous CDS alerts ranged from75.68% (February 2004) to 100.00% (December 2003), with the one-year average of 88.31% after CDS implementation (Figure 8).

Figure 8 Compliance with synchronous alerts for ACE and ARB during hyperkalemia



As the potential indirect effect of the synchronous CDS alert, the alert rate of the real-time asynchronous CDS increased from 12.1% to 12.5% after CDS implementation, but the difference was not statistically different (p = 0.752) (TABLE VI).

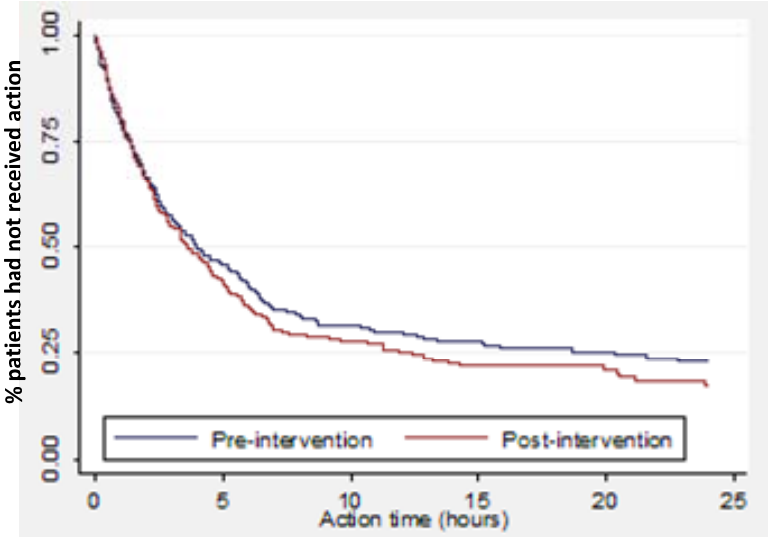
TABLE VI ALERT RATE OF REAL-TIME ASYNCHRNOUS [K+]↔ACE/ARB ALERTS

	Pre-intervention	Post-intervention	P-value
Total ACE and ARB orders	1947	1725	0.752
Orders alerted by asynchronous CDS	236	215	
Alert rate	12.1%	12.5%	

4.1.3 Modulators of Action Time and Time to Normal [K+]

The Kaplan-Meier estimates of the survival curves showed that the action time did not differ much during the first 3 hours after CDS implementation (Figure 8). Actions were taken more promptly after the 5th hour during the post-intervention period, even though the Log-rank test was not significant (p = 0.313).

Figure 9 Survival curves of action time for [K+]↔ACE/ARB[a]



[a] Action time was censored at 24 hour

In the Cox proportional hazards regression analysis, -2Log Likelihood was 3547.984 for model with ethnicity variables, and 3548.383 for model without ethnicity variables, and the p-value for the Chi-square test was 0.819. Since the ethnicity variables were not significant, and the coefficient estimates of other covariates did not differ after removing ethnicity variables from the model, the model without ethnicity variables was selected as the final model for interpretation.

According to the regression results, the action time, after controlling for all the covariates, did not change significantly after CDS implementation. The clinicians' action time decreased as patient [K+] level increased (HR = 1.51 with $p = 0.003$ for 5.7 mEq/L ≤ [K+] ≤ 6.0 mEq/L, and HR = 1.87 with $p < 0.0001$ for [K+] ≥ 6.1 mEq/L). Alerts from ICU patients were responded more promptly than patients from general medical or surgical units (HR = 1.38, $p = 0.032$). However, the action time was not associated patient age, gender, ethnicity, creatinine clearance level, time of the alert, and whether being the first hyperkalemic episode during the admission.

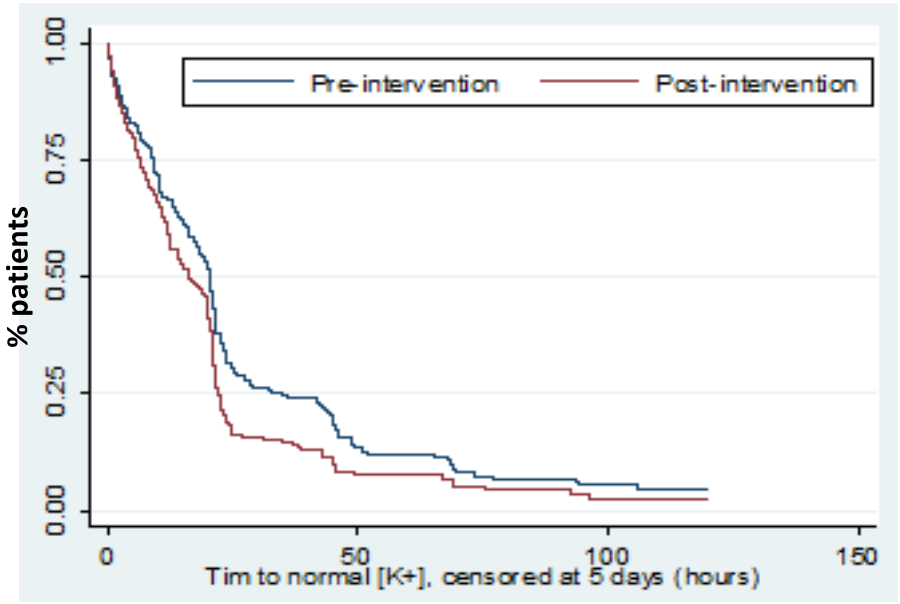
TABLE VII COX PROPORTIONAL HAZARDS REGRESSION ANALYSIS OF ACTION TIME FOR [K+]↔ACE/ARB

Variable	Coeff.	S.E.	HR	P-value
Intervention	0.10	0.11	1.11	0.356
Patient Characteristics				
Age				
1-19	0.20	0.74	1.22	0.784
20-44	0.00	0.19	1.00	0.983
45-64	-0.13	0.12	0.88	0.292
≥65	Referent			
Gender				
Male	Referent			
Female	0.003	0.12	1.00	0.979
Alert content				
[K+] level				
5.3-5.6	Referent			
5.7-6.0	0.41	0.14	1.51	0.003
6.1 and above	0.62	0.14	1.87	<0.0001
Creatinine clearance				
>85 for female, >95 for male	-0.13	0.19	0.88	0.495
85/95 - 26	Referent			
≤25	0.09	0.15	1.10	0.547
Alert frequency				
Not first episode	-0.19	0.28	0.83	0.493
Work flow incorporation				
Service location				
Medical/surgical	Referent			
ICU	0.32	0.15	1.38	0.032
Time of the alert				
Midnight - <7am	-0.14	0.16	0.87	0.371
7am - <5pm	Referent			
5pm - <Midnight	-0.10	0.19	0.91	0.599

It took less time for [K+] to return to normal for the post-intervention period than for the pre-intervention period (p = 0.0104) (Figure 10). After adjusting for all the covariates, the difference was still significant (p = 0.004) (TABLE VIII). The log-likelihood ratio test indicated

that the model without ethnicity variable was preferred as compared to the model with ethnicity variable (p = 0.444).

Figure 10 Survival curves of time to normal [K+] for [K+]↔ACE/ARB



Similar to clinicians' response time, patient time to normal [K+] also decreased as alerting [K+] level increased (HR = 1.48 with p = 0.003 for 5.7 mEq/L ≤ [K+] ≤ 6.0 mEq/L, and HR = 1.73 with p < 0.0001 for [K+] ≥ 6.1 mEq/L). It took less time for patients with normal creatinine clearance level than those with impaired renal function (HR = 1.71, p = 0.002), but not significant longer for patients with severe renal insufficiency (HR = 0.90, p = 483). Patient time to normal [K+] was also longer if the patient had previous hyperkalemic episode during the

hospital stay (HR = 0.40, p = 0.002). Alerts from ICU patients and alert time between 5pm and midnight were also significantly associated with decreased time to normal [K+]. However, patient age, gender, and ethnicity had no effect on the patient time to normal [K+].

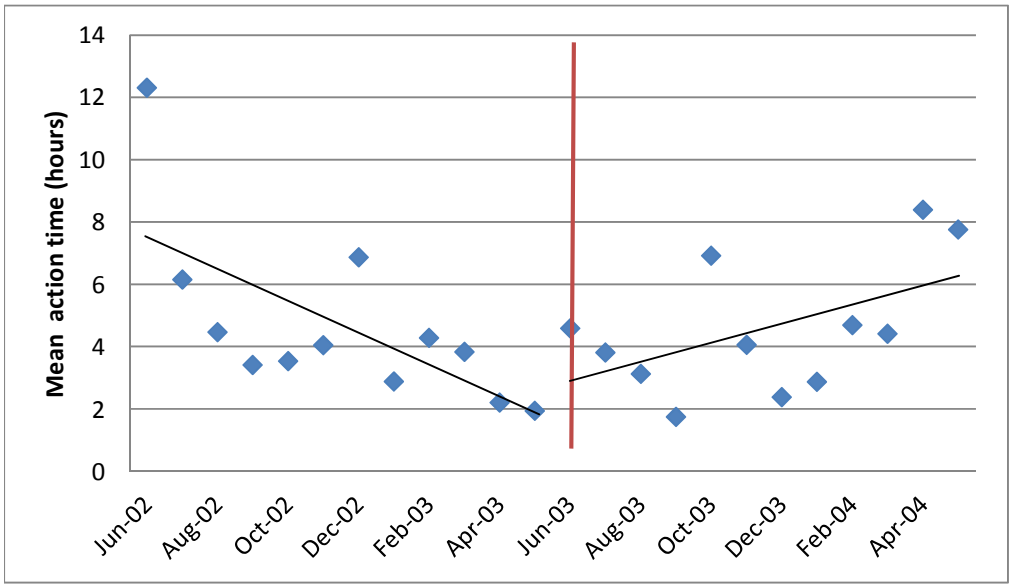
TABLE VIII COX PROPORTIONAL HAZARDS REGRESSION ANALYSIS OF PATIENT TIME TO NORMAL [K+] FOR [K+]↔ACE/ARB

Variable	Coeff.	S.E.	HR	P-value
Intervention	0.31	0.11	1.37	0.004
Patient characteristics				
Age				
1-19	1.31	0.74	3.72	0.077
20-44	-0.22	0.19	0.80	0.238
45-64	-0.09	0.12	0.91	0.428
≥65	Referent			
Gender				
Male	Referent			
Female	-0.07	0.11	0.94	0.547
Alert content				
[K+] level				
5.3-5.6	Referent			
5.7-6.0	0.39	0.13	1.48	0.003
6.1 and above	0.55	0.14	1.73	<0.0001
Creatinine clearance				
>85 for female, >95 for male	0.53	0.17	1.71	0.002
85/95 - 26	Referent			
≤25	-0.11	0.15	0.90	0.483
Alert frequency				
Not first episode	-0.92	0.30	0.40	0.002
Work flow incorporation				
Service location				
Medical/surgical	Referent			
ICU	0.41	0.15	1.50	0.008
Time of the alert				
Midnight - <7am	-0.13	0.16	0.88	0.416
7am - <5pm	Referent			
5pm - <Midnight	0.60	0.18	1.83	0.001

4.2.4 Effect of Real-time Asynchronous Alert

The monthly median action time was shown in Figure 11. The maximum median action time was 12.3 hours in June 2002 and the minimum median action time was 1.7 hours in September 2003. There seemed to be a drop after CDS implementation, but the monthly variation was too large to draw any firm conclusion.

Figure 11 Time series of mean action time with



Segmented regression model was used to evaluate the effect of the asynchronous alert while controlling for the covariates. The Durbin-Watson statistics was 1.9689 for model with ethnicity variable and 1.9829 for model without ethnicity variable. The AR(1) autocorrelation

coefficient was not significant in either model (p = 0.689 and 0.822). Therefore, no adjustment was done for autocorrelation.

The model estimates using ordinary least squares methods were reported in TABLE IX. The p-value from the partial F-test was 0.514. Again, the model parameter estimates and the associated p-value did not differ much after excluding the ethnicity variables. Thus, the ethnicity variables were not included in the final model.

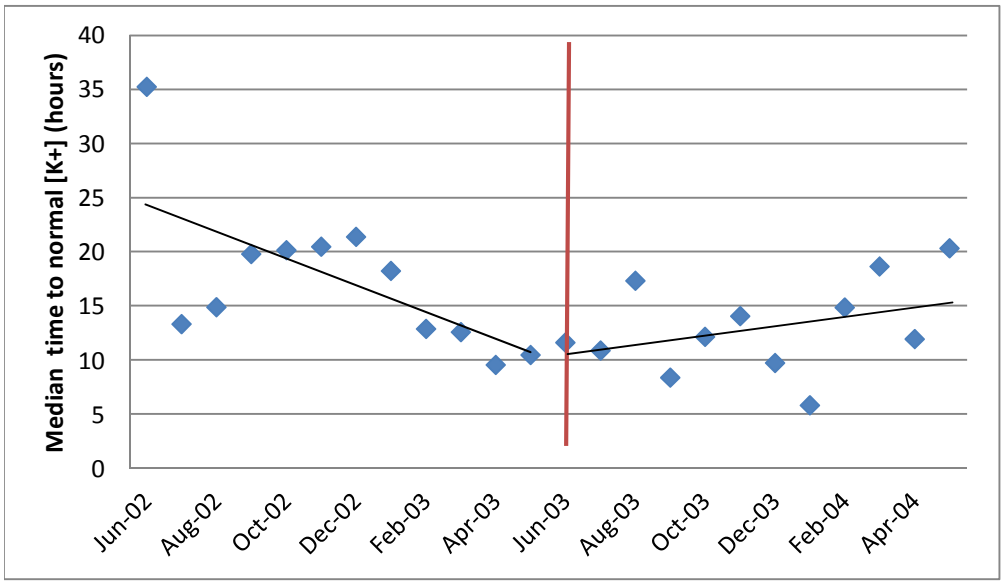
The coefficient estimates were not significant for either the difference in the intercept (p = 0.196) or the difference in the slope (p = 0.158). This indicated that there was no significant reduction right after the intervention or any changes in the trend. Thus, the segmented regression analysis confirmed that the real-time asynchronous CDS alerts implemented in June 2003 had no effect in reducing the clinicians' action time when managing hyperkalemia among ACE/ARB users. Similar to the Cox proportional hazards model results, the reduction in clinicians' action increased as [K+] increased. The coefficient estimate for 5.7 mEq/L ≤ [K+] ≤ 6.0 mEq/L was -2.22 (p = 0.016), and the coefficient estimate for the critical value of 6.1 mEq/L and above was -3.24 (p = 0.001).

TABLE IX SEGMENTED REGRESSION ANALYSIS OF [K+]↔ACE/ARB ACTION TIME

Variable	Coeff.	S.E.	P-value
Intercept	8.84	1.43	<0.0001
Slope for pre-intervention	-0.10	0.16	0.536
Difference in intercept	-1.92	1.49	0.196
Difference in the slope	0.33	0.23	0.158
Patient Characteristics			
Age			
1-19	-0.62	5.58	0.912
20-44	-0.85	1.31	0.518
45-64	0.40	0.81	0.619
≥65	Referent		
Gender			
Male	Referent		
Female	0.42	0.77	0.587
Alert content			
[K+] level			
5.3-5.6	Referent		
5.7-6.0	-2.22	0.92	0.016
6.1 and above	-3.24	0.94	0.001
Creatinine clearance			
>85 for female, >95 for male	1.28	1.23	0.300
85/95 - 26	Referent		
≤25	-0.12	1.05	0.912
Alert frequency			
First episode	Referent		
Not first episode	1.43	1.81	0.431
Work flow incorporation			
Service location			
Medical/surgical	Referent		
ICU	-1.80	1.06	0.091
Time of the alert			
Midnight - <7am	1.59	1.07	0.141
7am - <5pm	Referent		
5pm - <Midnight	0.88	1.30	0.501

The monthly median patient time to normal [K+] were plotted in Figure 12, ranging from 35.2 hours in June 2002 to 5.8 hours in January 2004. The Durbin-Watson statistics was 1.9858 for model with ethnicity variable and 2.0042 for model without ethnicity variable. Since the AR(1) coefficient estimate was not significant in either model (p = 0.896 and 0.934), autocorrelation was not adjusted in the final model. The model estimates using ordinary least squares methods were reported in TABLE X. Since the p-value from the partial F-test was 0.326, the ethnicity variables were not included in the final model.

Figure 12 Time series of mean patient time to normal [K+]



Even though the intervention indicator was significant in the Cox proportional hazards model for time to normal [K+], the difference for the intercept and slope were not statistically

significant in the segmented regression analysis ($p = 0.134$ for the difference in intercept, $p = 0.487$ for difference in the slope). The results showed that the asynchronous alert did not help to reduce patient time to normal [K+] for ACE/ARB users. Besides that, variables such as [K+] between 5.7-6.0 mEq/L, alerts from ICU, and alert time between 5pm and midnight were significantly associated with reduced time to normal [K+] in the Cox proportional hazards model, but not in the segmented regression analysis.

TABLE X SEGMENTED REGRESSION ANALYSIS OF [K+]↔ACE/ARB PATIENT TIME TO NORMAL [K+]

Variable	Coeff.	S.E.	P-value
Intercept	24.03	3.96	<0.0001
Slope for pre-intervention	-0.06	0.45	0.903
Difference in intercept	-6.18	4.12	0.134
Difference in the slope	0.45	0.65	0.487
Patient Characteristics			
Age			
1-19	-10.62	15.47	0.493
20-44	1.81	3.62	0.618
45-64	0.19	2.24	0.932
≥65	Referent		
Gender			
Male	Referent		
Female	2.79	2.14	0.193
Alert content			
[K+] level			
5.3-5.6	Referent		
5.7-6.0	-4.32	2.55	0.091
6.1 and above	-7.22	2.60	0.006
Creatinine clearance			
>85 for female, >95 for male	-5.90	3.41	0.084
85/95 - 26	Referent		
≤25	0.48	2.92	0.871
Alert frequency			
First episode	Referent		
Not first episode	15.75	5.02	0.002
Work flow incorporation			
Service location			
Medical/surgical	Referent		
ICU	-1.50	2.94	0.611
Time of the alert			
Midnight - <7am	-1.41	2.98	0.636
7am - <5pm	Referent		
5pm - <Midnight	-6.72	3.62	0.064

4.2 [K+]↔K-sup

4.2.1 Patient characteristics and Descriptive Statistics

The real-time asynchronous alert was fired on 506 admissions during the post-intervention period. If such CDS alerts were in place during the pre-intervention period, 600 admissions would have been fired (TABLE XI). The mean age for those patients was 53.63 years and 54.93 years for the pre- and post-intervention samples, respectively. Less than half of the patients were male. Only 20.8% of the pre-intervention sample and 29.3% of the post-intervention sample were non-Hispanic, while the Hispanic patients consisted of 6.2% of the pre-intervention sample and 7.9% of the post-intervention sample. The two patient populations did not differ with respect to age and gender. However, the ethnicity breakdown was significantly different (p = 0.001).

TABLE XI K-SUP PATIENT CHARACTERISTICS FOR REAL-TIME ASYNCHRONOUS ALERTS

	Pre-intervention (n = 600)	Post-intervention (n = 506)	p-value
Age (year), mean [s.e.]	53.63 [20.75]	54.93 [20.39]	0.296
1-19	9.3% (56)	7.5% (38)	0.510
20-44	17.2% (103)	19.8% (100)	
45-64	40.3% (242)	38.7% (196)	
≥65	33.2% (199)	34.0% (172)	
Male	48.2% (289)	45.5% (230)	0.368
Ethnicity			
Non-Hispanic	20.8% (125)	29.3% (148)	0.001
Hispanic	6.2% (37)	7.9% (40)	
Unknown	73.0% (438)	62.9% (318)	

There were 989 potential asynchronous alerts fired on 3740 K-sup orders (26.4 alerts per 100 K-sup orders) during the pre-intervention period, and 859 true alerts fired on 3677 K-sup orders (23.4 alerts per 100 K-sup orders) during the post-intervention period (TABLE XII). There was no significant difference between pre- and post-intervention asynchronous alerts in terms of alert time, [K+] level, creatinine clearance level, whether being the first hyperkalemic episode during the admission, and service location. However, the post-intervention alerts fired on more K-sup orders than the pre-intervention ones did ($p < 0.0001$). At the order level, the alerted orders were cancelled more promptly during the post-intervention period with the mean action time of 6.73 hours (s.e. = 5.85) while the mean action time for the pre-intervention period was 8.65 hours (s.e. = 6.21). But fewer than 20% of the orders were cancelled within 24 hours after the asynchronous alert. Therefore, the action time until K-sup cancellation were censored at 48 hours after alert time for the regression analysis. The mean action time until K-sup cancellation was 14.4 hours (s.e. = 11.75) during the pre-intervention period as compared to 13.0 hours (s.e. = 12.17) during the post-intervention period, and the difference was statistically significant ($p = 0.016$). After counting repeating [K+] as another action besides K-sup cancelation, 92.3% of the alerted orders during the pre-intervention period and 89.3% of the alerted orders during the post-intervention period were acted upon within 24 hours after alert time. However, the mean action time until K-sup cancellation or repeating [K+] increased from 10.61 hours (s.e.=7.96) during the pre-intervention period to 12.62 hours (s.e.=8.42) during the post-intervention period ($p < 0.0001$). Moreover, the mean patient time to normal [K+] was also longer during the post-intervention period (mean =23.50 hours, s.e. = 20.80) than during the pre-intervention period (mean = 21.37 hours, s.e. = 22.72).

TABLE XII DESCRIPTIVE STATISTICS FOR REAL-TIME ASYNCHRNOUS [K+]↔K-SUP ALERTS

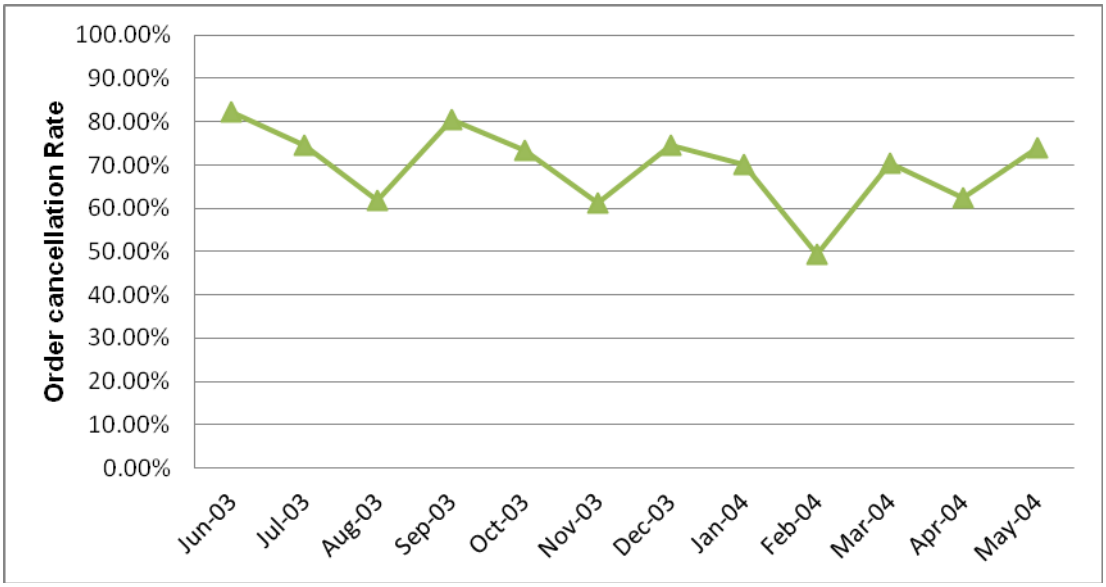
Variables	Pre-intervention	Post-intervention	P-value
Alert-level	n = 989	n = 859	
Time of the alert			0.419
Midnight - <7am	32.0% (316)	31.8% (273)	
7am - <5pm	54.1% (535)	56.2% (483)	
5pm - <Midnight	14.0% (138)	12.0% (103)	
[K+] level			0.692
5.0-5.3	51.6% (510)	51.5% (442)	
5.4-6.0	37.3% (369)	36.2% (311)	
6.1 and above	11.1% (110)	12.3% (106)	
Creatinine clearance (eGFR not available at the time)			0.560
>85 for female, >95 for male	20.1% (177)	20.5% (164)	
85/95 - 26	53.9% (475)	55.7% (447)	
≤25	26.1% (230)	23.8% (191)	
First episode	60.7% (600)	58.9% (506)	0.441
Alerted on more than 1 order	53.3% (527)	63.1% (542)	<0.0001
Service location			0.541
Medical/surgical	64.3% (633)	63.0% (537)	
ICU	35.7% (351)	37.1% (316)	
Order-level	n = 3740	n = 3677	
Action time (hour), mean [s.e.][a]			
Until K-sup cancellation (censored at 24hr)	8.65 [6.21]	6.73 [5.85]	<0.0001
Censored cases	81.5% (3049)	82.7% (3040)	0.408
Until K-sup cancellation (censored at 48hr)	14.4 [11.75]	13.0 [12.17]	0.016
Censored cases	75.6% (2829)	76.8% (2823)	0.252
Until K-sup cancellation or repeat [K+]	10.61 [7.96]	12.62 [8.42]	<0.0001
Censored cases	7.7% (288)	10.7% (394)	<0.0001
Time to normal [K+] (hour), mean [s.e.][a]	21.37 [22.72]	23.50 [20.80]	0.0004
Censored after 5 days	24.8% (928)	31.8% (1169)	<0.0001

[a] Calculated based on uncensored cases.

4.2.2 Effect of Synchronous CDS Alert

The K-sup cancellation rate after receiving the synchronous CDS alert ranged from 49.28% in February 2004 to 82.14% in June 2003, with 1-year average rate of 69.46% (Figure 13).

Figure 13 Compliance with synchronous alerts for K-sup during hyperkalemia



Fewer K-sup orders were alerted by the asynchronous CDS alert after CDS implementation (28.8% vs. 30.4%, p = 0.005), which indicated an indirect effect of the synchronous alerts (TABLE XIII).

TABLE XIII ALERT RATE OF REAL-TIME ASYNCHRNOUS [K+]↔K-SUP ALERTS

	Pre-intervention	Post-intervention	P-value
Total K-sup orders	12519	12551	0.005
Orders alerted by asynchronous CDS	3806	3611	
Alert rate	30.4%	28.8%	

4.2.3 Modulators of Action Time and Time to Normal [K+]

K-sup orders were cancelled more promptly during the first 10 hours after receiving the asynchronous alert, and less promptly afterwards (Figure 14). And the Log-rank test showed

that the difference between the pre- and post-intervention was statistically significant (p = 0.0001). For action time to either K-sup cancellation or repeating [K+], the alerted K-sup orders were responded more promptly during the pre-intervention period than the post-intervention period (p < 0.0001) (Figure 15).

Figure 14 Survival curves for time until K-sup cancellation, censored at 48 hours

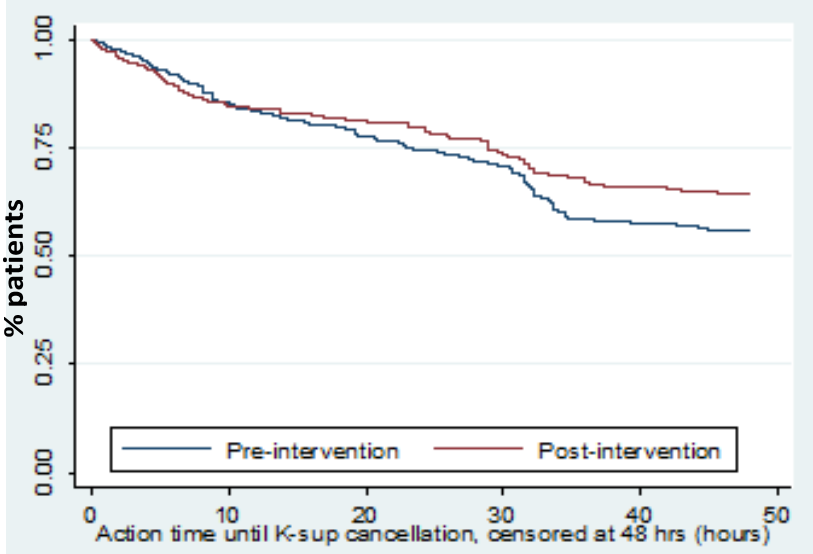
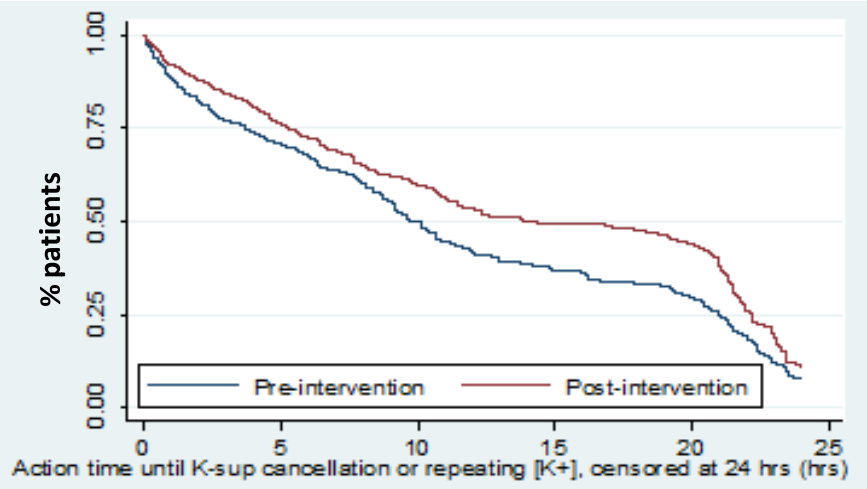


Figure 15 Survival curves for time until K-sup cancellation or repeating [K+], censored at 24 hours



When comparing the Cox proportional hazards models for action time until K-sup cancellation, the log-likelihood ratio test for whether or not to include ethnicity variables was significant with p-value less than 0.0001. Therefore, the model with the ethnicity variables was selected as the final model. Despite the significant difference from the Log-rank test, the action time until K-sup cancellation did not change after the implementation of the asynchronous alert (HR = 1.00, p = 0.938) while controlling for all the covariates. While [K+] level ≥ 5.4 mEq/L and having unknown ethnicity were associated with decreased action time till K-sup cancellation, □ □ □ □ □ □ □□·½□□Ĥ□□ □]□□Ũ□Ā□□□ˢ□□ᵞ痻ʒ̀ 嚆

normal creatinine clearance level, not being the first hyperkalemic episode, being alerted on multiple K-sup orders, and alert time outside of normal day shift were associated with prolonged action time until K-sup cancellation.

TABLE XIV COX PROPORTIONAL HAZARDS REGRESSION ANALYSIS OF TIME TO K-SUP CANCELLATION, CENSORED AT 48 HOURS

Variable	Coeff.	S.E.	HR	P-value
Intervention	-0.004	0.05	1.00	0.938
Patient characteristics				
Age				
1-19	0.39	0.31	1.48	0.214
20-44	0.06	0.08	1.07	0.448
45-64	-0.07	0.06	0.93	0.211
≥65	Referent			
Gender				
Male	Referent			
Female	-0.37	0.05	0.69	<0.0001
Ethnicity				
Non-hispanic	Referent			
Hispanic	-0.18	0.14	0.83	0.188
Unknown	0.26	0.07	1.29	<0.001
Alert content				
[K+] level				
5.0-5.3	Referent			
5.4-6.0	0.46	0.06	1.59	<0.0001
6.1 and above	1.50	0.07	4.48	<0.0001
Creatinine clearance				
>85 for female, >95 for male	-0.38	0.08	0.68	<0.0001
85/95 - 26	Referent			
≤25	0.09	0.06	1.10	0.118
Alert frequency				
Not first episode	-0.12	0.05	0.89	0.026
Alerted on more than 1 order	-0.59	0.07	0.55	<0.0001
Work flow incorporation				
Service location				
Medical/surgical	Referent			
ICU	-0.11	0.06	0.89	0.076
Time of the alert				
Midnight - <7am	-0.57	0.06	0.56	<0.0001
7am - <5pm	Referent			
5pm - <Midnight	-0.30	0.09	0.74	0.001

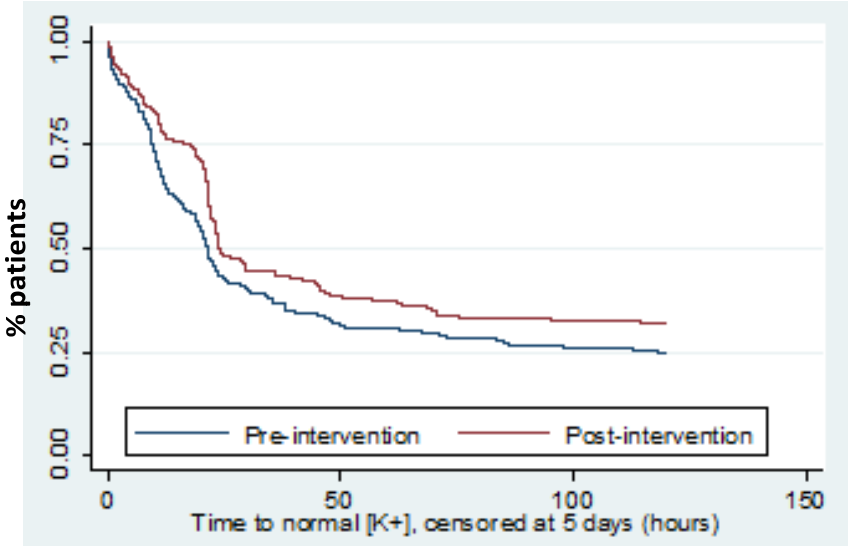
The Log-likelihood ratio test for Cox proportional hazards models of time to K-sup cancellation or repeating [K+] was not significant ($p = 0.062$). Additionally, the action time was not significantly different for Hispanic patients ($p = 0.086$) and patients with unknown ethnicity ($p = 0.505$) when comparing with non-Hispanic patients. Therefore, the model without ethnicity variables was selected. After counting repeating [K+] as one of the actions in responding to hyperkalemia for K-sup users, it took clinicians longer time to cancel K-sup or repeat [K+] after the implementation of the asynchronous CDS alert ($HR = 0.85$, $p < 0.0001$) while controlling for all the covariates (TABLE XV). When counting repeating [K+] as another action, aged 20-44 years and 45-64 years were both associated with shortened action time as compared to aged 65 and older. Being male, having [K+] higher than 5.3, having normal renal function or severe renal insufficiency, and being the first alert during the admission and located in ICU were significantly associated with shorter action time. It was worth noting that it took longer time to respond to alerts fired between midnight and 7am ($HR = 0.48$, $p < 0.0001$), but shorter respond time for alerts fired between 5pm to midnight ($HR = 1.54$, $p < 0.0001$).

TABLE XV COX PROPORTIONAL HAZARDS REGRESSION ANALYSIS OF TIME TO K-SUP CANCELLATION OR REPEATING [K+], CENSORED AT 24 HOURS

Variable	Coeff.	S.E.	HR	P-value
Intervention	-0.16	0.03	0.85	<0.0001
Patient characteristics				
Age				
1-19	0.10	0.13	1.10	0.465
20-44	-0.10	0.04	0.91	0.017
45-64	-0.08	0.03	0.92	0.007
≥65	Referent			
Gender				
Male	Referent			
Female	-0.18	0.03	0.84	<0.0001
Alert content				
[K+] level				
5.0-5.3	Referent			
5.4-6.0	0.31	0.03	1.36	<0.0001
6.1 and above	1.73	0.04	5.66	<0.0001
Creatinine clearance				
>85 for female, >95 for male	0.08	0.03	1.09	0.013
85/95 - 26	Referent			
≤25	0.07	0.03	1.08	0.029
Alert frequency				
Not first episode	-0.10	0.03	0.90	<0.001
Alerted on more than 1 order	0.05	0.05	1.05	0.249
Work flow incorporation				
Service location				
Medical/surgical	Referent			
ICU	0.69	0.03	1.99	<0.0001
Time of the alert				
Midnight - <7am	-0.73	0.03	0.48	<0.0001
7am - <5pm	Referent			
5pm - <Midnight	0.43	0.04	1.54	<0.0001

The survival curves for patient time to normal [K+] using Kaplan-Meier estimate methods showed that it took longer for patient to reach normal [K+] after CDS implementation, and the difference between pre-intervention and post-intervention was significant ($p < 0.0001$) (Figure 16). Even after adjusting for all the covariates, the multivariate regression analysis results also suggested prolonged patient time to normal [K+] after CDS implementation (TABLE XVI).

Figure 16 Survival curves for time to normal [K+], censored at 5 days



After comparing the Log-likelihood of the Cox proportional hazards model with and without ethnicity variables, the ethnicity variables were kept in the final model given that the p-value of the Log-likelihood ratio tests was 0.015. For patients aged between 20-44 years, with [K+] ≥ 6.1 mEq/L, normal renal function, being alerted on multiple K-sup orders, located in ICU, alerted between 5pm to midnight, it took shorter time for

them to reach normal [K+] again. However, patients with severe renal insufficiency, had multiple hyperkalemic episodes during the admission, and being alerted during midnight to 7am, the time to reach normal [K+] was significantly longer.

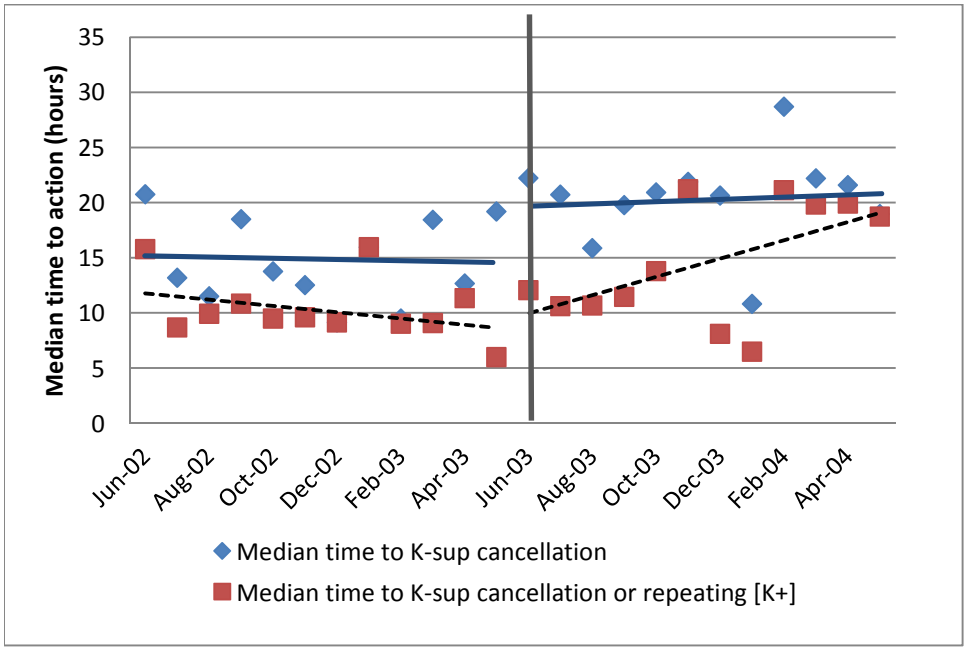
TABLE XVI COX PROPORTIONAL HAZARDS REGRESSION ANALYSIS OF TIME TO NORMAL [K+], CENSORED AT 5 DAYS

Variable	Coeff.	S.E.	HR	P-value
Intervention	-0.21	0.03	0.81	<0.0001
Patient characteristics				
Age				
1-19	0.24	0.13	1.27	0.081
20-44	0.09	0.05	1.10	0.044
45-64	-0.03	0.03	0.97	0.396
≥65	Referent			
Gender				
Male	Referent			
Female	0.06	0.03	1.06	0.059
Ethnicity				
Non-hispanic	Referent			
Hispanic	0.11	0.07	1.11	0.143
Unknown	-0.07	0.04	0.93	0.097
Alert content				
[K+] level				
5.0-5.3	Referent			
5.4-6.0	0.01	0.03	1.02	0.644
6.1 and above	0.12	0.05	1.13	0.015
Creatinine clearance				
>85 for female, >95 for male	0.50	0.04	1.65	<0.0001
85/95 - 26	Referent			
≤25	-0.52	0.04	0.59	<0.0001
Alert frequency				
Not first episode	-0.60	0.03	0.55	<0.0001
Alerted on more than 1 order	0.16	0.05	1.17	0.002
Work flow incorporation				
Service location				
Medical/surgical	Referent			
ICU	0.78	0.04	2.19	<0.0001
Posting time of the lab test				
Midnight - <7am	-0.12	0.04	0.89	0.001
7am - <5pm	Referent			
5pm - <Midnight	0.39	0.05	1.48	<0.0001

4.2.4 Effect of Real-time Asynchronous Alert

The mean time to K-sup cancellation and to K-sup cancellation or repeating [K+] was calculated based on the uncensored cases using a monthly interval (Figure 17). The monthly mean time to K-sup cancellation ranged from 7.4 hours in June 2003 to 19.4 hours in June 2002. When repeating [K+] was also counted as one of the actions, the mean time to action decreased for most of the months before CDS implementation, except for January 2003, but only for July, August, and December of Year 2003 after CDS implementation. Despite the monthly variation for mean time to K-sup cancellation, there seemed to be a descending trend □ 莒:葡 搒┌▯ 薪□葭□摧ì ć┐ □□□observational period.

Figure 17 Time series of mean time to action for K-sup patients



The multivariate segmented regression model was used to evaluate the effect of asynchronous CDS alert. The Durban-Watson statistics was 0.5333 for model with ethnicity variables, and 0.5332 for model without ethnicity variables. The AR(1) coefficient estimate was significant in both models ($p < 0.0001$). Therefore, autocorrelation was adjusted in the final model. The maximum likelihood estimates method was used to estimate the model parameters. The Log-likelihood ratio test suggested that the ethnicity variables should be included.

While controling for all the covariates at the individual level, neither the difference in intercept nor the difference in the slope was statistically different. This indicated that the real-time asynchronous alerts had little effect in reducing time to K-sup order cancellation. Similar to the Cox proportional regression results, clinicians' time to cancel K-sup order decreased as [K+] level increased given the negative and statistically significant coefficient estimates for [K+] 5.7-6.0mEq/L and above 6.0 mEq/L. It took the clinicians longer time to cancel K-sup for patients aged 45-64 years, being female, and Hispanic, and shorter time for patients with unknow ethnicity. The time to K-sup cancellation was shorter for patients with normal [K+] level (coeff. = -1.79, $p = 0.001$), but longer for patients with severe renal insufficiency (coeff. = 3.24, $p < 0.0001$), which conflicted with the Cox proportional hazards model. Moreover, action time to K-sup cancellation was shorter for ICU patients, and longer for alerts fired on multiple K-sup orders and those fired between midnight and 7am.

TABLE XVII SEGMENTED REGRESSION ANALYSIS OF TIME TO K-SUP CANCELLATION

Variable	Coeff.	S.E.	P-value
Intercept	20.95	1.74	<0.0001
Slope for pre-intervention	-0.09	0.21	0.672
Difference in intercept	2.78	2.10	0.186
Difference in the slope	0.07	0.30	0.815
AR(1)	-0.77	0.01	<0.0001
Patient Characteristics			
Age			
1-19	2.65	1.46	0.070
20-44	0.95	0.67	0.157
45-64	1.98	0.52	<0.001
≥65	Referent		
Gender			
Male	Referent		
Female	0.95	0.45	0.035
Ethnicity			
Non-hispanic	Referent		
Hispanic	1.96	0.98	0.045
Unknown	-1.26	0.54	0.018
Alert content			
[K+] level			
5.3-5.6	Referent		
5.7-6.0	-3.62	0.39	<0.0001
6.1 and above	-10.84	0.62	<0.0001
Creatinine clearance			
>85 for female, >95 for male	-1.79	0.54	0.001
85/95 - 26	Referent		
≤25	3.84	0.57	<0.0001
Alert frequency			
Not first episode	-0.79	0.43	0.064
Alerted on multiple K-sup orders	3.24	0.49	<0.0001
Work flow incorporation			
Service location			
Medical/surgical	Referent		
ICU	-6.17	0.51	<0.0001
Time of the alert			
Midnight - <7am	3.13	0.48	<0.0001
7am - <5pm	Referent		
5pm - <Midnight	-1.06	0.60	0.075

The segmented regression models for action time until K-sup cancellation or repeating [K+] were assessed using the same model selection methods. After comparing the Durbin-Watson statistics, AR(1) coefficient estimates, and Log-likelihood test, the model with ethnicity variables was selected. Most of the model estimates were very similar to those from the model for action time to K-sup cancellation (TABLE XVIII). After counting repeating [K+] as one of the actions, alert time between 5pm and midnight was associated with shorter action time (coeff. = -2.63, $p < 0.0001$), which was also observed in the Cox proportional hazards model (TABLE XV).

TABLE XVIII SEGMENTED REGRESSION ANALYSIS OF TIME TO K-SUP CANCELLATION OR REPEATING [K+]

Variable	Coeff.	S.E.	P-value
Intercept	14.00	0.77	<0.0001
Slope for pre-intervention	-0.09	0.09	0.312
Difference in intercept	0.52	0.89	0.560
Difference in the slope	0.23	0.13	0.068
AR(1)	-0.70	0.01	<0.0001
Patient Characteristics			
Age			
1-19	2.04	0.81	0.012
20-44	-0.04	0.36	0.918
45-64	0.75	0.27	0.006
≥65	Referent		
Gender			
Male	Referent		
Female	1.24	0.24	<0.0001
Ethnicity			
Non-hispanic	Referent		
Hispanic	1.62	0.53	0.002
Unknown	-0.50	0.29	0.083
Alert content			
[K+] level			
5.3-5.6	Referent		
5.7-6.0	-2.78	0.21	<0.0001
6.1 and above	-9.35	0.33	<0.0001
Creatinine clearance			
>85 for female, >95 for male	-0.23	0.29	0.424
85/95 - 26	Referent		
≤25	1.36	0.30	<0.0001
Alert frequency			
Not first episode	0.08	0.23	0.714
Alerted on multiple K-sup orders	1.47	0.27	<0.0001
Work flow incorporation			
Service location			
Medical/surgical	Referent		
ICU	-4.17	0.27	<0.0001
Time of the alert			
Midnight - <7am	2.89	0.25	<0.0001
7am - <5pm	Referent		
5pm - <Midnight	-2.63	0.32	<0.0001

It took an average of 24.0 hours for the [K+] level to get back to normal after the asynchronous CDS were alerted on K-sup users. The monthly mean ranged greatly between each month from June 2002 to May 2004 with minimum of 12.0 hours in December 2002 and maximum of 35.1 hours in May 2003 (Figure 18).

Figure 18 Time series of mean time to normal [K+] for K-sup patients

After applying the model selection criteria, the model with ethnicity variables and AR(1) variance structure was selected. According to the segmented regression results, the positive and significant slope for the pre-intervention period suggested an upward trend before CDS implementation (coeff. = 1.69, p = 0.024). Even though the asynchronous alert did not decrease patient time to normal [K+] immediately after implementation (p = 0.588), there was a significant difference in the slope (coeff. = -2.50, p = 0.019). This indicated not only a reduction in outcome,

but also a declining trend during the post-intervention period since the post-intervention slope estimate was negative. (TABLE XVIII)

Similar to the Cox proportional hazards regression results, female gender, high [K+] level, normal creatinine clearance level, and alert from ICU were associated with shorter time to normal [K+], while younger age and unknown ethnicity was associated with longer time to normal [K+]. Discrepancy was observed between the segmented regression results and Cox proportional hazards model regarding the alert time. Even though it took patients with alerts fired between 5pm and midnight shorter time to have [K+] level back to normal from both regressions, alerts fired between midnight and 7pm took shorter time to reach normal [K+] in the segmented regression model (coeff. = -3.90, $p = 0.002$), but longer time in the Cox proportional hazards model (HR = 0.89, $p = 0.001$).

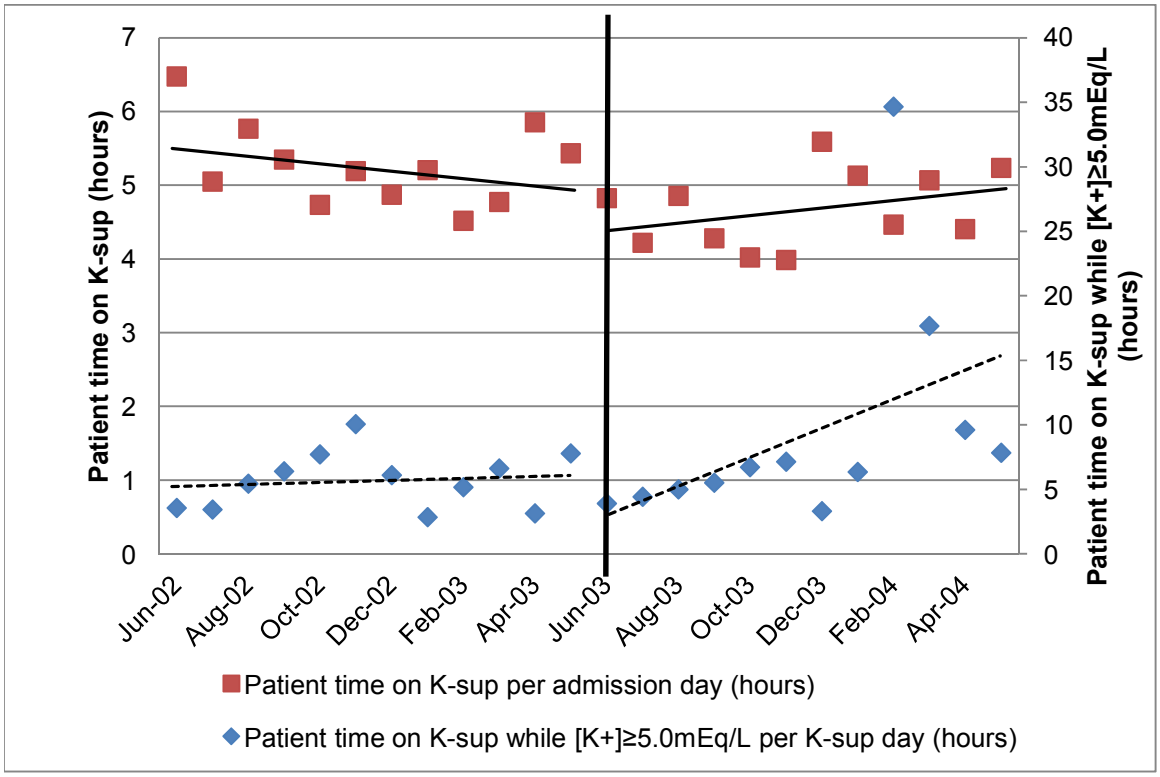
TABLE XIX SEGMENTED REGRESSION ANALYSIS OF TIME TO NORMAL [K+] FOR K-SUP

Variable	Coeff.	S.E.	P-value
Intercept	39.97	5.94	<0.0001
Slope for pre-intervention	1.69	0.75	0.024
Difference in intercept	4.03	7.44	0.588
Difference in the slope	-2.50	1.07	0.019
AR(1)	-0.84	0.01	<0.0001
Patient Characteristics			
Age			
1-19	4.41	3.70	0.234
20-44	4.75	1.74	0.007
45-64	7.90	1.36	<0.0001
≥65	Referent		
Gender			
Male	Referent		
Female	-5.81	1.18	<0.0001
Ethnicity			
Non-Hispanic	Referent		
Hispanic	3.14	2.52	0.212
Unknown	3.01	1.38	0.029
Alert content			
[K+] level			
5.3-5.6	Referent		
5.7-6.0	-6.98	0.99	<0.0001
6.1 and above	-16.51	1.61	<0.0001
Creatinine clearance			
>85 for female, >95 for male	-5.11	1.40	<0.001
85/95 - 26	Referent		
≤25	6.99	1.47	<0.0001
Alert frequency			
Not first episode	17.46	1.10	<0.0001
Alerted on multiple K-sup orders	1.72	1.23	0.160
Work flow incorporation			
Service location			
Medical/surgical	Referent		
ICU	-23.39	1.33	<0.0001
Time of the alert			
Midnight - <7am	-3.90	1.23	0.002
7am - <5pm	Referent		
5pm - <Midnight	-15.84	1.54	<0.0001

4.2.5 The Combined Effect of Synchronous and Real-time Asynchronous CDS

As shown in Figure 19, the monthly average (mean) of patient time on K-sup per patient admission day ranged from 3.98 hours in November 2003 to 6.47 hours in June 2002, and it gradually declined over the study period. The Durbin-Watson statistics was 1.976, and the AR(1) coefficient estimates was not significant (p = 0.708). Therefore, autocorrelation was not adjusted. According to the ordinary least square estimates for the segmented regression model, neither the difference in the intercept nor the difference in the slope was significant (TABLE XX). This indicated that the declining trend that was observed in Figure 19 was consistent after the implementation of the CDS alerts. In other words, the synchronous and real-time asynchronous alerts did not have significant effect on patient time on K-sup.

Figure 19 Time series of patient time on K-sup, June 2002-May 2004



After normalized on patient time on K-sup, the monthly average for patient time on K-sup while [K+] was elevated was around 5 hours per day, but with a peak of 34.6 hours in February 2004 (Figure 19). The segmented regression results suggested that no significant change either in the slope or in the intercept occurred after CDS implementation (TABLE XXI). The Durbin-Watson statistics was 1.736 for ordinary least square estimates, and 1.841 for maximum likelihood estimates.

TABLE XX SEGMENTED REGRESSION ANALYSIS OF PATIENT TIME ON K-SUP PER ADMISSION DAY

	Ordinary Least Square Estimates			Maximum Likelihood Estimates		
Variable	Coeff.	S.E.	P-value	Coeff.	S.E.	P-value
Intercept	5.59	0.33	<0.0001	5.56	0.31	<0.0001
Slope for pre-intervention	-0.05	0.04	0.274	-0.05	0.04	0.288
Difference in intercept	0.10	0.06	0.137	0.09	0.06	0.136
Difference in the slope	-0.63	0.44	0.165	-0.64	0.43	0.154
AR(1)	-	-	-	0.09	0.23	0.708
Durbin-Watson statistics	1.976			1.817		
R-square	0.332			0.360		

TABLE XXI SEGMENTED REGRESSION ANALYSIS OF PATIENT TIME ON K-SUP WHILE [K+] WAS ELEVATED

	Ordinary Least Square Estimates			Maximum Likelihood Estimates		
Variable	Coeff.	S.E.	P-value	Coeff.	S.E.	P-value
Intercept	5.05	3.72	0.190	4.96	4.11	0.243
Slope for pre-intervention	0.10	0.51	0.852	0.11	0.56	0.847
Difference in intercept	1.02	0.71	0.169	0.97	0.80	0.240
Difference in the slope	-4.13	4.96	0.415	-4.06	5.39	0.461
AR(1)	-	-	-	-0.10	0.24	0.692
Durbin-Watson statistics	1.736			1.841		
R-square	0.262			0.224		

4.3 Effect of the Once Daily Report

Based on the distribution of [K+] level for inpatients at UIH during the period of January 2009 – June 2009, the cutoffs of ≥5.1 mEq/L and ≥5.5 mEq/L were chosen for the once daily report of [K+]↔K-sup and [K+]↔ACE/ARB, respectively. The time analysis of the [K+] posting time suggested that the best time to run the daily report would be between 9am and 10am, which was about 1 to 2 hours after most of the [K+] from the morning routine testing were posted. The report, if run during this time period, would have the potential to capture most of the hyperkalemic cases if not attended already, and minimize patient time in danger as [K+] was elevated. After discussion with the pharmacy department and the clinical safety team, the time of 2pm was chosen given the workflow of the existing practice.

During the period of June 28th 2011 – October 3rd 2011, the once daily report fired 51 [K+]↔ACE/ARB alerts on 34 patients, and 44 [K+]↔K-sup alerts on 32 patients. This equaled to 0.56 [K+]↔ACE/ARB alerts and 0.45 [K+]↔K-sup alerts per day for a 450-bed hospital like UIH. The patient characteristics and descriptive statistics of the alerts were summarized in TABLE XXII. The [K+] level of the majority of the alerts were between 5.5-5.6 mEq/L (47.1%) and between 5.7-6.0 mEq/L (35.3%) for [K+]↔ACE/ARB, and between 5.1-5.6 mEq/L (88.6%) for [K+]↔K-sup. Most of the alerts fired on patients with impaired renal function or severe renal insufficiency, and patients from general medical or surgical unit. Over 70% of the alerts were from [K+] drawn between midnight and 7am, for both [K+]↔ACE/ARB and [K+]↔K-sup.

TABLE XXII PATIENT CHARACTERISTICS AND DESCRIPTIVE STATISTICS FOR ONCE DAILY REPORT, JUNE 28 2011 – OCTOBER 3 2011

	[K+]↔ACE/ARB	[K+]↔K-sup
Patient level	n = 34	n=32
Age (year), mean [s.e.]	57.78 [16.68]	49.46 [21.02]
1-19	2.9% (1)	12.5% (4)
20-44	14.7% (5)	21.9% (7)
45-64	50.0% (17)	40.6% (13)
≥65	32.4% (11)	25.0% (8)
Alert level	n = 51	n = 44
[K+] level		
5.1/5.5-5.6	47.1% (24)	88.6% (39)
5.7-6.0	35.3% (18)	9.1% (4)
6.1 and above	17.6% (9)	2.3% (1)
Creatinine clearance		
>85	13.7% (7)	34.1% (15)
85 - 26	39.2% (20)	47.7% (21)
≤25	47.1% (24)	18.2% (8)
Service location		
Medical/surgical	94.1% (48)	65.9% (29)
ICU	5.9% (3)	34.1% (15)
Time of [K+]		
Midnight - <7am	72.6% (37)	72.7% (32)
7am - <5pm	13.7% (7)	27.3% (12)
5pm - <Midnight	13.7% (7)	0.0% (0)

After excluding the censored cases, the monthly mean time to K-sup cancellation ranged from 3.86 hours in September 2010 to 21.68 hours in October 2010. And the mean time to K-sup cancellation or repeating [K+] was between 7.32 hours (January 2011) and 17.09 hours (March 2011). The time to K-sup cancellation seemed to decrease after the implementation of the once daily report in May 2010, but with large variations between each month (Figure 18). However, the decrease was not statistically significant after adjusting for all the covariates (TABLE XXIII). The significant coefficient estimate for the difference in the slope and the negative slope for the post-intervention period indicated that there was a descending trend in action time to K-sup cancelation after once daily report was implemented.

As shown in Figure 20, the action time to K-sup cancelation or repeating [K+] had an ascending trend during the pre-intervention period and a descending trend afterwards. After controlling for the covariates, only the difference in the slope was significant (coeff. = -0.44, p = 0.001). The segmented regression estimates did not confirm the ascending trend for the pre-intervention period, but did ascertain the impact of once daily report in gradually reducing time to either cancel the K-sup order or repeat [K+].

Based on the model selection criteria, the model with ethnicity variables and AR(1) autocorrelation structure fitted the data better than other models for both action time to K-sup cancellation and action time to K-sup cancellation or repeating [K+].

Figure 20 Time series of mean time to action for K-sup patients, May 2009-April 2011

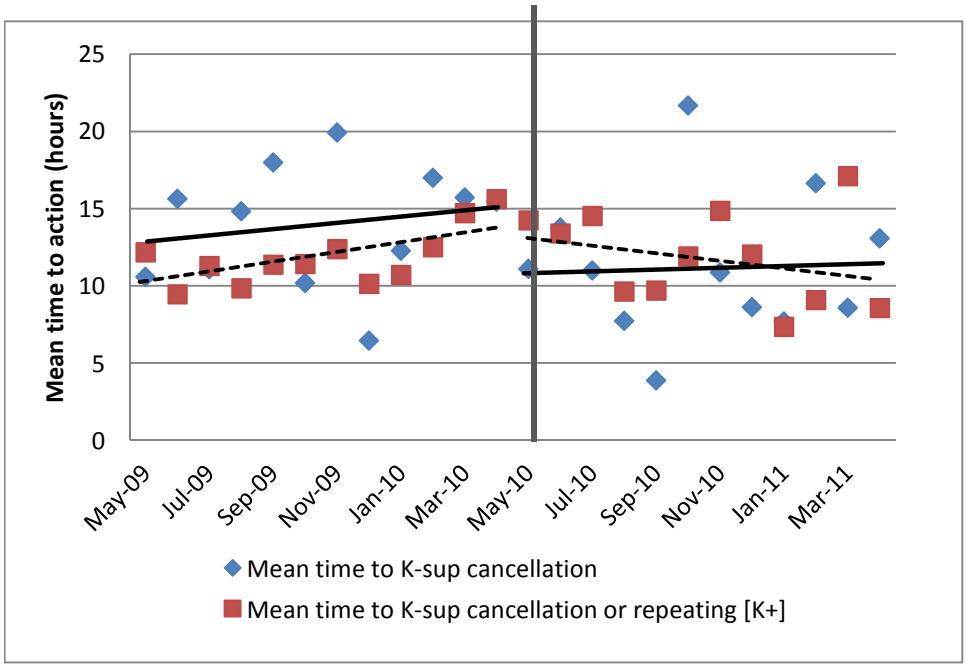


TABLE XXIII SEGMENTED REGRESSION ANALYSIS OF TIME TO K-SUP CANCELLATION, MAY 2009-APRIL 2011

Variable	Coeff.	S.E.	P-value
Intercept	25.61	1.80	<0.0001
Slope for pre-intervention	0.03	0.21	0.892
Difference in intercept	2.42	1.89	0.199
Difference in the slope	-0.76	0.32	0.019
AR(1)	-0.81	0.01	<0.0001
Patient Characteristics			
Age			
1-19	-9.35	1.15	<0.0001
20-44	-0.52	0.71	0.462
45-64	-0.77	0.56	0.173
≥65	Referent		
Gender			
Male	Referent		
Female	-1.31	0.48	0.007
Ethnicity			
Non-hispanic	Referent		
Hispanic	-0.75	0.63	0.236
Unknown	6.57	1.26	<0.0001
Alert content			
[K+] level			
5.3-5.6	Referent		
5.7-6.0	-2.93	0.39	<0.0001
6.1 and above	-7.48	0.76	<0.0001
Creatinine clearance			
>85 for female, >95 for male	2.25	0.61	0.000
85/95 - 26	Referent		
≤25	0.28	0.57	0.623
Alert frequency			
Not first episode	-2.26	0.42	<0.0001
Alerted on multiple K-sup orders	1.88	0.50	0.000
Work flow incorporation			
Service location			
Medical/surgical	Referent		
ICU	-5.93	0.54	<0.0001
Time of the alert			
Midnight - <7am	-0.75	0.50	0.134
7am - <5pm	Referent		
5pm - <Midnight	-2.69	0.54	<0.0001

TABLE XXIV SEGMENTED REGRESSION ANALYSIS OF TIME TO K-SUP CANCELLATION OR REPEATING [K+], MAY 2009-APRIL 2011

Variable	Coeff.	S.E.	P-value
Intercept	15.44	0.79	<0.0001
Slope for pre-intervention	0.12	0.09	0.181
Difference in intercept	0.68	0.85	0.421
Difference in the slope	-0.44	0.13	0.001
AR(1)	-0.73	0.01	<0.0001
Patient Characteristics			
Age			
1-19	-4.92	0.65	<0.0001
20-44	-0.99	0.39	0.010
45-64	-1.31	0.31	<0.0001
≥65	Referent		
Gender			
Male	Referent		
Female	-0.36	0.26	0.168
Ethnicity			
Non-hispanic	Referent		
Hispanic	0.16	0.34	0.642
Unknown	2.42	0.69	0.001
Alert content			
[K+] level			
5.3-5.6	Referent		
5.7-6.0	-2.45	0.22	<0.0001
6.1 and above	-6.84	0.42	<0.0001
Creatinine clearance			
>85 for female, >95 for male	1.32	0.33	<0.0001
85/95 - 26	Referent		
≤25	0.00	0.31	0.998
Alert frequency			
Not first episode	0.06	0.23	0.783
Alerted on multiple K-sup orders	0.81	0.28	0.004
Work flow incorporation			
Service location			
Medical/surgical	Referent		
ICU	-4.60	0.29	<0.0001
Time of the alert			
Midnight - <7am	1.08	0.27	<0.0001
7am - <5pm	Referent		
5pm - <Midnight	-2.83	0.30	<0.0001

Figure 21 illustrates that patient time to normal [K+] increased monotonically between January 2010 and July 2010, which was followed by an over-all declining but variant trend. However, after controlling for the covariates, neither the difference in intercept nor the difference in the slope was significant (TABLE XXV).

Figure 21 Time series of mean time to normal [K+] for K-sup patients, May 2009-April 2011

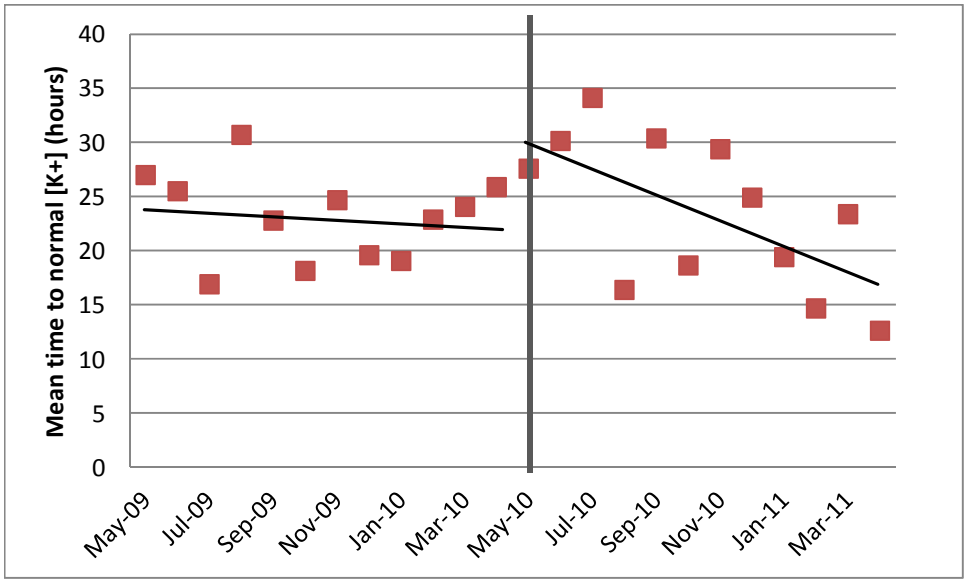


TABLE XXV SEGMENTED REGRESSION ANALYSIS OF TIME TO NORMAL [K+], MAY 2009-APRIL 2011

Variable	Coeff.	S.E.	P-value
Intercept	62.78	6.13	<0.0001
Slope for pre-intervention	0.29	0.73	0.693
Difference in intercept	1.94	6.13	0.752
Difference in the slope	-1.92	1.12	0.088
AR(1)	-0.84	0.01	<0.0001
Patient Characteristics			
Age			
1-19	5.29	3.31	0.110
20-44	5.45	2.06	0.008
45-64	-0.11	1.63	0.946
≥65	Referent		
Gender			
Male	Referent		
Female	-2.14	1.42	0.132
Ethnicity			
Non-hispanic	Referent		
Hispanic	8.74	1.85	<0.0001
Unknown	0.27	3.67	0.941
Alert content			
[K+] level			
5.3-5.6	Referent		
5.7-6.0	-7.03	1.13	<0.0001
6.1 and above	-9.06	2.21	<0.0001
Creatinine clearance			
>85 for female, >95 for male	1.42	1.78	0.426
85/95 - 26	Referent		
≤25	1.26	1.67	0.449
Alert frequency			
Not first episode	16.22	1.21	<0.0001
Alerted on multiple K-sup orders	-5.31	1.45	<0.0001
Work flow incorporation			
Service location			
Medical/surgical	Referent		
ICU	-15.26	1.58	<0.0001
Time of the alert			
Midnight - <7am	-5.63	1.45	<0.0001
7am - <5pm	Referent		
5pm - <Midnight	-11.75	1.55	<0.0001

The integrated monthly patient time on K-sup and patient time on K-sup while [K+] was elevated were also analyzed using the segmented regression. After normalized on total patient

admission days, the once daily report did not have influence in shortening patient time on K-sup, either in the monthly mean estimates or the segmented regression analysis. The Durbin-Watson statistics was 1.667 using the ordinary least square estimates. The once daily report did not have an immediate effect on patient time on K-sup since the difference in the slope estimate was insignificant. The difference in the slope was significant when autocorrelation was not adjusted ($p = 0.034$). The positive estimate of slope difference yielded positive slope for the post-intervention period, which indicated that the patient time on K-sup increased after once daily report was implemented. After adjusting the autocorrelation using AR(1) variance structure, the difference in the slope was still marginally significant ($p = 0.058$).

The monthly average for patient time on K-sup while [K+] was elevated varied by each month after normalized on patient time on K-sup of the same period (Figure 22). There was a drop from 12.7 hours per patient day in April 2010 to 5.6 hours in May 2010, which was reflected in the segmented regression analysis as the difference in the intercept was significant using ordinary least square estimates ($p = 0.045$) and marginal significant using maximum likelihood estimates ($p = 0.080$). Given the poor fit of the model (R-square = 0.2106), it was difficult to affirm the effect of once daily report in reducing patient time on K-sup while [K+] was elevated.

Figure 22 Time series of patient time on K-sup, May 2009-April 2011

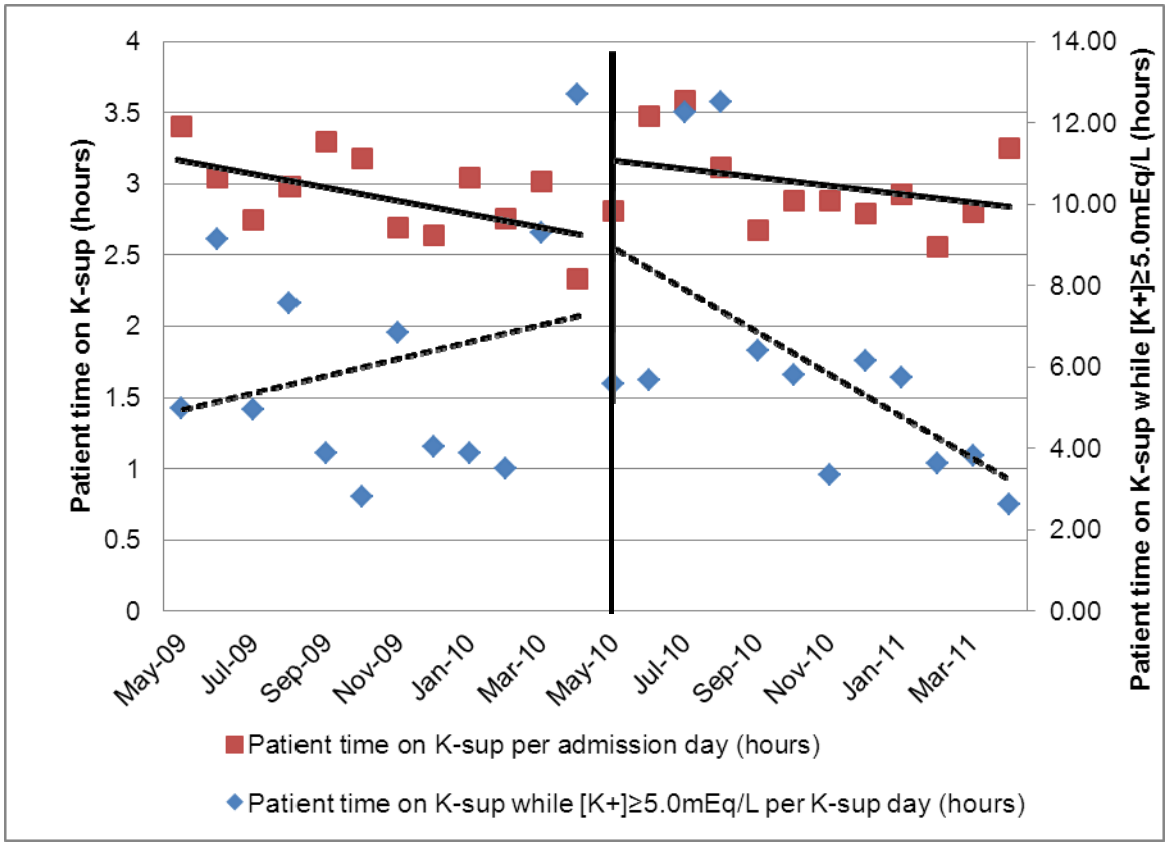


TABLE XXVI SEGMENTED REGRESSION ANALYSIS OF PATIENT TIME ON K-SUP PER ADMISSION DAY, MAY 2009-APRIL 2011

	Ordinary Least Square Estimates			Maximum Likelihood Estimates		
Variable	Coeff.	S.E.	P-value	Coeff.	S.E.	P-value
Intercept	3.248	0.175	<0.0001	3.260	0.197	<0.0001
Slope for pre-intervention	-0.049	0.024	0.051	-0.051	0.027	0.074
Difference in intercept	0.018	0.034	0.605	0.022	0.039	0.576
Difference in the slope	0.529	0.233	0.034	0.521	0.258	0.058
AR(1)	-	-	-	-0.113	0.252	0.659
Durbin-Watson statistics	1.666			1.732		
R-square	0.240			0.215		

TABLE XXVII SEGMENTED REGRESSION ANALYSIS OF PATIENT TIME ON K-SUP WHILE [K+]≥5.0mEq/L PER K-SUP DAY, MAY 2009-APRIL 2011

	Ordinary Least Square Estimates			Maximum Likelihood Estimates		
Variable	Coeff.	S.E.	P-value	Coeff.	S.E.	P-value
Intercept	4.711	1.774	0.015	4.423	2.081	0.047
Slope for pre-intervention	0.218	0.241	0.376	0.283	0.289	0.340
Difference in intercept	-0.730	0.341	0.045	-0.738	0.398	0.080
Difference in the slope	2.128	2.365	0.379	1.120	2.900	0.704
AR(1)	-	-	-	-0.147	0.251	0.565
Durbin-Watson statistics	1.806			1.881		
R-square	0.211			0.163		

5. DISCUSSION

5.1 Discussion of the Effect of the CDS Alerts

This study aimed to examine the effect of the laboratory-pharmacy linkage CDS alerts in improving clinicians' action time and patient outcomes related to inpatient hyperkalemia. In general, the clinicians' compliance with the synchronous alerts was 88.31% for [K+]↔ACE/ARB and 69.46% for [K+]↔K-sup, which was similar to previous reported acceptance rate for interruptive drug-drug interaction alerts in inpatient settings.[68] Without the synchronous CDS, those cancelled orders likely would have been prescribed until the next time [K+] was checked. As the indirect effect of the asynchronous CDS alerts, the alert rate of the real-time asynchronous CDS for [K+]↔K-sup dropped significantly after CDS implementation. Although the alert rate did not change significantly for [K+]↔ACE/ARB, which could because of the insufficient sample size, the high compliance rate of the synchronous alert would be strong and sufficient evidence for the effect of synchronous CDS in changing clinicians' behavior and improving patient safety.

As suggested by the segmented regression analysis, the asynchronous alerts had limited influence on accelerating clinicians' action for both [K+]↔ACE/ARB and [K+]↔K-sup. This could because of the stronger effect of the synchronous CDS which was implemented at the same time. The clinicians' were more aware of the hyperkalemic situation if the synchronous alert was previously fired on the same patient. In addition, the suboptimal communication mode might also explain the lack of benefit from the asynchronous CDS. Back in year 2003 and 2004, CDS was still an evolving technology. Multiple communication channels were deployed to deliver the CDS alerts in fear of miscommunication or delayed communication. However, the multi-channel communication approach, which included script messages to the designated nursing station, inpatient pharmacy, and to the electronic clinical inbox, resulted in

communication chaos that blurred responsibility. Nevertheless, the asynchronous alert had a lasting effect on reducing patient time to normal [K+] for K-sup users. Such benefit was not observed for ACE/ARB users.

The synchronous and real-time asynchronous alerts, together, have limited effect on the integrated outcomes of patient time on K-sup after normalization. Given the large volume of K-sup orders in inpatient setting, the potential benefit of the CDS alerts could have been diluted.

The segmented regression using the data from May 2009 to April 2011 showed significant drop in patient time on K-sup while [K+] was elevated right after the implementation of once daily report, and a lasting effect of reducing clinicians' action time for K-sup users during the post-intervention period. However, it was arguable whether the once daily report truly had such a substantial causal effect given the low alert frequency. There were 3166 K-sup orders prescribed between June 28th 2010 and October 3rd 2010, as compared to 32 K-sup orders being alerted during the same time period in 2011. Moreover, the poor model fit for the segmented regression of patient time on K-sup could also make the conclusion less robust.

5.2 Discussion of the Modulators for Action Time and Time to Normal [K+]

As stated as Objective 2, this study examined the impact of patient characteristics, alert content, alert frequency, and work flow incorporation, in changing the time course of managing inpatient hyperkalemia. There were inconsistent and sometimes conflicting findings from the Cox proportional hazards models and segmented regression models. The Cox proportional hazards model censors the cases that did not reach the study end point or were lost to follow up. Censoring those cases has the advantage of making full use of the available information when estimating time-to-event type of outcomes.[107] Therefore, the estimates from the Cox proportional hazards model were favored when assessing the impact of the factors on clinicians' action time and patient time to normal [K+].

Based on the Cox proportional hazards model estimates, patient characteristics including age, gender, and ethnicity were often insignificantly associated with action time or time to normal [K+], except for the positive relationship between female gender and prolonged action time for K-sup patients. Despite those inconsistent and most of the time insignificant findings, increased [K+] level were associated with shortened action time for both [K+]↔ACE/ARB and [K+]↔ K-sup (TABLE XXVIII). Moreover, clinicians responded more promptly to patients with impaired renal function, given that HR for normal vs. impaired renal function was 0.88 for [K+]↔ACE/ARB ($p = 0.495$) and 0.68 for time to K-sup cancellation ($p < 0.0001$). And the action time decreased further if the patient had severe renal insufficiency as suggested by HR being great than 1 for severe renal insufficiency vs. impaired renal function for both [K+]↔ACE/ARB and [K+]↔K-sup. Even though the association between the renal function and the action time was not significant for [K+]↔ACE/ARB and severe renal insufficiency vs. impaired renal function for time till K-sup cancellation, the severity of renal impairment was consistently associated with shortened action time for both [K+]↔ACE/ARB and [K+]↔K-sup. These findings echoed the findings from previous studies regarding the importance of alert severity and the clinical risk in clinicians' responses when receiving the CDS alerts.[68] There was a dramatic decrease in clinicians' action for cases with [K+] ≥ 6.0 mEq/L vs. those with [K+] ≤ 6.0 mEq/L as suggested by HR of 1.87for [K+]↔ACE/ARB ($p < 0.0001$), 4.48 for time till K-sup cancellation ($p < 0.0001$), and 5.56 for time till K-sup cancellation or repeating [K+] ($p < 0.0001$). The shortened action time could be because of the devoted attention from the clinicians, and could also result from the confounding effect of critical reporting mechanism.

For the factors that represented alert frequency, not being the first hyperkalemia episode was not significant in predicting action time for [K+]↔ACE/ARB, but was significantly associated with longer time until K-sup cancellation. The positive relationship remained the same after counting repeating [K+] as another action. Similarly, alerting on multiple K-sup order was also a

significant factor for prolonged action time to cancel K-sup orders. It was conceivable that clinicians might be aware of the hyperkalemic situation after the first alert and decided to postpone any clinical intervention, or modify one of the K-sup orders but not all if the alert fired on multiple orders. Despite those possible explanations, the possible association also suggested that alert frequency could have negative effect on clinicians prompt response to hyperkalemia. Additionally, ACE/ARB users from ICU and [K+]↔K-sup alerts fired during the normal day shift would be responded more promptly than their counterparts, which indicated the influence of the work flow on the time to action and the importance of considering appropriate incorporation of CDS into existing clinical practice.

Being the patient-centered outcome, time to normal [K+] depended both on clinicians' rapid response and on patient's renal function. Therefore, patient time to normal [K+] was hypothesized to be associated with both alert severity and renal function. The association between increased [K+] level and decreased time to normal [K+], while controlling for all the covariates, could be the result of reduced action time for cases with higher [K+] level. This also indicated the indirect effect of the asynchronous CDS alert in improving patient outcome. Impaired renal function was associated with increased time until [K+] went back to normal, which justified clinicians' consideration of renal function when responding to the asynchronous alerts.

It was noticeable that more factors in the regression model were significant for [K+]↔K-sup than for [K+]↔ACE/ARB. Besides the difference in clinicians' practice pattern and patient outcome, the difference in the sample size could be another explanation. At UIH, K-sup, including potassium-containing hyperalimentation, IV fluids, and oral tables, was more often prescribed than ACE inhibitors and ARB. Moreover, dialysis patients were excluded in the [K+]↔ACE/ARB sample, but not in the [K+]↔K-sup sample.

5.3 Discussion of Alert Frequency

Not being the first episode during admission and being alerted on multiple K-sup orders were used to evaluate the effect of alert frequency on action time and patient time to normal [K+] for K-sup patients. It is arguable that alert frequency is not a good proxy for alert fatigue if the alerts did not alert the same clinician and without knowing how many other non-potassium related alerts were fired. Such information was not available and was out of the scope of this study. Given the data limitation, this study was not able to obtain alert frequency at clinician level. Even though alert fatigue was shown as a strong predictor for delayed clinical action in published literature, the effect of alert frequency on clinician action time should not be interpreted as the effect of alert fatigue.

The Cox proportional hazards regression analysis showed that not being the first episode was significantly associated with increased physician action time for the [K+]↔K-sup alerts and patient time to normal [K+]. Since having the following alerts depends on the resolve of previous episode, there might be a systematic difference in physician action time and patient time to normal [K+] between first hyperkalemia episode and the following ones. Therefore, stratified analysis was conducted to address the concern. In TABLE XXXII, action time and time to normal [K+] during the post-intervention period was always longer for the following episodes than for the first episodes. During the pre-intervention period, only the mean action time to cancel K-sup orders was faster within first 24 hours for the first episodes (i.e. action time censored at 24 hours was 6.36 hours vs. 9.96 hours). It took longer during the first episodes than during the follow episodes, for the clinicians to cancel K-sup orders during first 48 hours, to cancel K-sup or repeat [K+], or for the patient to get back to normal [K+].

5.4 Analytical Framework for Evaluating CDS Intervention

Another specific aim for this study was to demonstrate the analytical approach for evaluating the effect of CDS interventions. This included choosing the appropriate outcome measurement and relative analysis methods correspondingly. Outcomes were chosen deliberately depending on the availability for measurement. For example, no confirmative step was built in the system to accurately record clinicians' acceptance or ignorance when receiving the synchronous alert. Therefore, the compliance rate was defined as having no medication order placed within one hour after the alert time, which was accomplished by matching the medication orders with the synchronous alerts data. The one-hour time frame was an arbitrary decision, but this definition was the most practical way of measuring compliance rate given the availability of the data.

Selecting the appropriate outcomes also presented challenge for measuring the effect of asynchronous alert on clinicians' action time for [K+]↔K-sup. Even though repeating [K+] could also be an expected action in response to hyperkalemia, [K+] was the part of the routine morning laboratory tests for most inpatients. Without a definite algorithm to distinguish the routine morning [K+] from the re-checks, counting repeating [K+] as the action could have underestimated the true action time. This could explain the increase in the mean action time from 10.61 hours (s.e.=7.96) during the pre-intervention period to 12.62 hours (s.e.=8.42) during the post-intervention period when repeating [K+] was counted (TABLE XII). The increase could probably because of more alerts were fired between midnight and 7am during the pre-intervention period (14.0%) than during the post-intervention period (12.0%). Alerts that fired between midnight and before 7am would have been closer to the routine morning laboratory tests that were usually done daily at 6am.

Two outcomes were used as the measurement of the real-time asynchronous CDS alert, clinicians' action time and patient time to normal [K+]. According to the analytical framework,

clinicians' action time was the direct measurement of the effect while patient time to normal [K+] was affected by the asynchronous CDS indirectly. Although time to normal [K+] would generally be preferred in patient-centered outcomes research, its dependence on individual patient's pharmacokinetic response should be acknowledged while interpreting the effect of real-time asynchronous alert in improving patient outcomes.

Additionally, time to normal [K+] was also subject to measurement bias induced by testing frequency. It was conceivable that the higher the testing frequency, the sooner the normal [K+] would be observed. Therefore, even though the intervention had no significant effect in reducing patient time to normal [K+], the reduction might be statistically significant if [K+] were tested more frequently after CDS implementation. In order to address the concern about measurement bias, the [K+] testing frequency during June 2002 – May 2003 vs. June 2003 – May 2004 was compared for all patients using ACE inhibitors, ARB, and K-sup separately. No significant difference in the test rate per patient day using any of the three medications was observed after CDS implementation.

5.5 Study Limitations

The single group pre-post observational study design exposed this study to certain threats to internal validity. The pre-post study design assumes any change in the outcomes was resulted from the intervention. However, there could also be a historical change in clinicians' practice behavior that was totally irrelevant to the implementation of the CDS alerts. Moreover, the evolving HIT during the past decade presented the maturation threat to the study validity. The comparison of patient characteristics and other covariates were made for the pre-intervention sample vs. the post-intervention sample to address potential maturation of the patient population. Among other subtle changes, the major increase in the reporting rate of the

ethnicity variable was observed from the study period of 2002-2004 to 2009-2011 (TABLE IV, XI, and XXX).

Moreover, this study was conducted in one single urban academic teaching hospital, with a large proportion of black and Hispanic patients. The practice pattern and patient constitution at UIH are not necessarily representative of other medical institutions. Therefore, the findings from this study lack generalizability.

Patient time to normal [K+] was used as a measurement for patient outcome. However, its validity and reliability in predicting true clinical outcomes, such as mortality and ADE rate, were difficult to establish because of the non-linear association between [K+] level and cardiac risk and the variance in individual tolerance of high serum potassium. For inpatients under bedside monitoring and other alerting mechanisms like CDS alerts and critical value reporting, severe adverse events related to hyperkalemia were rare. Therefore, a large sample size was required in order to detect any statistically significant changes.

As suggested by other studies, the complexity of the clinical situation was one of the factors impact clinicians' response to CDS alerts. However, only [K+] level and renal function were used to represent the clinical factors that were considered in managing hyperkalemia. Clinical decision making is a complicated cognitive process that involves weighting and balancing the benefits and risks. In a real clinical scenario, other biochemical and physiologic parameters, other medication use, and comorbidities were definitely considered as well. Hyperkalemia occurs very prevalently in inpatient settings, in various patient populations, and can be induced by diet, medication, or disease. Therefore, it was very difficult to measure and quantify all potential confounding factors, let alone stratifying different scenarios without losing statistical power. On the other hand, this limitation also presented challenges for future studies and opportunities for studying laboratory-pharmacy linkage CDS in specific patient population.

6 CONCLUSIONS

To summarize, clinicians complied with synchronous CDS alerts in managing hyperkalemia in inpatient settings. The real-time asynchronous alert failed to demonstrate its effect in accelerating clinicians' action, but had potential effect in improving patient outcomes for K-sup users. The once daily report was effective in detecting potentially hazardous situations that had not been corrected after real-time asynchronous alert. But its impact on changing clinicians' practice behavior and improving patient outcomes was difficult to establish given the rare alert rate.

After controlling for patient demographics, alert frequency, and work flow incorporation, alert content, as represented by [K+] level and renal function, was strongly associated with clinicians' action time. Besides that, multiple alerts could produce alert fatigue if alerting the same clinician and resulted in delayed actions and prolonged hazardous time for patients while being hyperkalemic. Hyperkalemia was managed more efficiently if it occurred in ICU and during normal day shift with higher clinician-to-patient ratio. These modulators for clinician's action time not only depicted the decision making of the clinicians, but also presented areas for quality improvement.

This study demonstrated a process for implementing three types of laboratory-pharmacy linkage CDS and the analytical approach for evaluating their effect. CDS systems have great potential in improving prescribing behavior and patient outcome, if implemented appropriately. As shown in this study, the implementation process involves many steps such as building the knowledge base, simulation analysis and estimation using historical data, work flow incorporation, and quantitative evaluation. More importantly, this process should be iterative. Findings from the assessment should be utilized to identify opportunities for further improvement. Further timely modifications should be made accordingly.

Issues related to the outcome measurement, analytical methods, and limitations were also discusses in this study in hope that the experience from this study would be of value for healthcare organizations and application and knowledge base vendors to delivery effective CDS systems, for policy makers to guide the development EHR, and for researchers to enrich the scientific evidence of HIT.

APPENDICES

Appendix A

TABLE XXVIII SUMMARY OF THE EFFECT OF SYNCHRONOUS ALERT, REAL-TIME ASYNCHRONOUS ALERT, AND ONCE DAILY REPORT

		[K+]↔ACE/ARB	[K+]↔K-sup
Effect of the synchronous CDS	Cancellation rate, mean (minimum-maximum)	88.31% (75.68%-100.00%)	69.46% (49.28%-82.14%)
	Alert rate of asynchronous CDS	-	(-): 28.8% vs. 30.4%
Effect of the real-time asynchronous CDS	Clinicians' action time	-	-*
	Patient time to normal [K+]	-	(-): Difference in the slope, negative slope for post-intervention period
The combined effect of both synchronous CDS	Patient time on K-sup per admission day	N/A	-
	Patient time on K-sup while [K+] ≥ 5.0 mEq/L per K-sup day	N/A	-
Effect of the once daily report	Clinicians' action time	N/A	(-): Difference in the slope, negative slope for post-intervention period*
	Patient time to normal [K+]	N/A	-
	Patient time on K-sup per admission day		(+): Difference in the slope, and positive slope for the post-intervention period
	Patient time on K-sup while [K+] ≥ 5.0 mEq/L per K-sup day		(-): Difference in the intercept

Note:

-: The effect was not statistically significant ($p \geq 0.05$).

N/A: The measurement was not available.

(-): Significant reduction in the outcome.

[a] Same for time till K-sup cancellation and time till K-sup cancellation or repeating [K+].

Appendix B

TABLE XXIX SUMMARY OF COX PROPORTIONAL HAZARDS REGRESSION RESULTS FOR FACTORS ASSOCIATED WITH CHANGED TIME COURSE

	Action time			Time to normal [K+]	
	Action time for [K+]↔ACE/ARB	Action time till K-sup cancellation	Action time till K-sup cancellation or repeating [K+]	ACE/ARB	K-sup
Patient Characteristics					
Age					
1-19	-	-	-	-	-
20-44	-	-	(+)	-	(-)
45-64	-	-	(+)	-	-
≥65 (referent)					
Gender					
Male (referent)					
Female	-	(+)	(+)	-	-
Ethnicity					
Non-hispanic (referent)					
Hispanic	N/A	-	N/A	N/A	-
Unknown	N/A	(-)	N/A	N/A	-
Alert content					
[K+] level					
5.3-5.6 (referent)					
5.7-6.0	(-)	(-)	(-)	(-)	-
6.1 and above	(-)	(-)	(-)	(-)	(-)
Creatinine clearance					
>85 for female, >95 for male	-	(+)	(-)	(-)	(-)
85/95 - 26 (referent)					
≤25	-	-	(-)	-	(+)
Alert frequency					
Not first episode	-	(+)	(+)	(+)	(+)
Alerted on multiple K-sup orders	N/A	(+)	-	N/A	(-)
Work flow incorporation					
Service location					
Medical/surgical (referent)					
ICU	(-)	-	(-)	(-)	(-)
Time of the alert					
Midnight - <7am	-	(+)	(+)	-	(+)
7am - <5pm (referent)					
5pm - <Midnight	-	(+)	(-)	(-)	(-)

Note:

-: The association was not statistically significant ($p \geq 0.05$).

(-): Significant and negative association, which means the factor was associated with shorten action time and shorten time to normal [K+]. It also means HR>1 in Cox proportional hazards model and negative coefficient estimates in segmented regression analysis.

N/A: The variable was not available or was not included in the final model.

Appendix C

TABLE XXX K-SUP PATIENT CHARACTERISTICS FOR REAL-TIME ASYNCHRONOUS ALERTS, MAY 2009 – APRIL 2011

	Pre-intervention (n = 443)	Post-intervention (n = 394)	p-value
Age (year), mean [s.e.]	51.95 [19.83]	54.78 [19.42]	0.038
1-19	8.8% (39)	6.1% (24)	0.510
20-44	21.7% (96)	17.3% (68)	
45-64	43.8% (194)	45.2% (178)	
≥65	25.7% (114)	31.5% (124)	
Male	44.2% (196)	44.2% (174)	0.981
Ethnicity			
Non-Hispanic	79.0% (350)	80.0% (315)	0.903
Hispanic	17.4% (77)	16.2% (64)	
Unknown	3.6% (16)	3.8% (15)	

Appendix D

TABLE XXXI DESCRIPTIVE STATISTICS FOR REAL-TIME ASYNCHRNOUS [K+]↔K-SUP ALERTS, MAY 2009 – APRIL 2011

Variables	Pre-intervention	Post-intervention	P-value
Alert-level	n =760	n = 696	
Posting time of the lab test			0.261
Midnight - <7am	49.7% (378)	54.0% (376)	
7am - <5pm	32.1% (244)	29.2% (203)	
5pm - <Midnight	18.2% (138)	16.8% (117)	
[K+] level			0.070
5.0-5.3	53.7% (408)	59.1% (411)	
5.4-6.0	39.7% (302)	33.9% (236)	
6.1 and above	6.6% (50)	7.0% (49)	
Creatinine clearance (eGFR not available at the time)			0.306
>85 for female, >95 for male	18.1% (133)	18.0% (121)	
85/95 - 26	61.0% (448)	57.7% (387)	
<=25	21.0% (154)	24.3% (163)	
First episode	58.3% (443)	56.6% (394)	0.517
Alerted on more than 1 order	42.8% (325)	40.7% (283)	0.417
Service location			0.004
Medical/surgical	67.0% (503)	73.9% (496)	
ICU	33.0% (248)	26.1% (175)	
Order-level	n = 2873	n = 2958	
Action time (hour), mean [s.e.]			
Until K-sup cancellation (censored at 24hr)	9.07 [5.62]	6.87 [5.44]	<0.0001
Censored cases	76.5% (2198)	79.6% (2355)	0.004
Until K-sup cancellation (censored at 48hr)	14.49 [11.10]	10.29 [9.79]	<0.0001
Censored cases	69.2% (1988)	76.1% (2250)	<0.0001
Until K-sup cancellation and repeat [K+]	11.73 [7.94]	11.49 [8.02]	0.271
Censored cases	8.0% (229)	9.2% (273)	0.087
Time to normal [K+] (hour), mean [s.e.]	23.25 [22.98]	22.98 [22.53]	0.7091
Censored after 5 days	36.5% (1048)	27.6% (815)	<0.0001

Appendix E

TABLE XXXII STRATIFIED ANALYSIS OF ACTION TIME AND TIME TO NORMAL [K+]

	First episode			Following episode		
	Pre	Post	P-value	Pre	Post	P-value
Action time (hour), mean [s.e.][a]						
Until K-sup cancellation (censored at 24hr)	6.36 [5.47]	4.75 [4.11]	0.0002	9.96 [6.24]	8.23 [6.49]	0.0001
Censored cases	84.2% (1337)	81.6% (1218)	0.054	79.5% (1712)	83.4% (1822)	0.001
Until K-sup cancellation (censored at 48hr)	14.71 [13.01]	9.81 [11.25]	<0.0001	14.20 [10.81]	15.13 [12.30]	0.190
Censored cases	76.6% (1215)	77.3% (1154)	0.605	75.0% (1614)	76.4% (1669)	0.276
Until K-sup cancellation or repeat [K+]	11.87 [8.28]	10.80 [8.49]	0.001	9.74 [7.62]	13.91 [8.12]	<0.0001
Censored cases	11.4% (181)	8.8% (132)	0.019	5.0% (107)	12.0% (262)	<0.0001
Time to normal [K+] (hour), mean [s.e.][a]	22.14 [23.31]	19.23 [19.15]	0.001	20.71 [22.20]	27.55 [21.49]	<0.0001
Censored after 5 days	18.7% (296)	18.2% (271)	0.727	29.4% (632)	41.1% (898)	<0.0001

[a] Calculated based on uncensored cases.

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VITA

Shengsheng (Sylvia) Yu, M.S., B. Pharm.

Department of Pharmacy Administration, College of Pharmacy, University of Illinois at Chicago
833 S. Wood St., Room 241 (MC 871), Chicago, IL 60612
Phone: 312-355-0711 E-mail: syu24@uic.edu

EDUCATION

2006	Zhejiang University, Hangzhou, Zhejiang, China Bachelor of Science in Pharmacy, College of Pharmaceutical Sciences Honors Degree in Business Administration: Intensive Training Program of Innovation and Entrepreneurship (ITP), Chu Kochen Honors College
2009	University of Illinois at Chicago, Chicago, IL Master of Science in Pharmacy Administration, College of Pharmacy. Thesis: *Determinants of cardio-protective dietary supplement use in US population: 1999-2004*. Research advisor: James Shaw, PhD, PharmD, MPH
2012	University of Illinois at Chicago (UIC), Chicago, IL Doctor of Philosophy in Pharmacy Administration, College of Pharmacy. Dissertation: *Linking laboratory and pharmacy: clinical decision support (CDS) to manage inpatient hyperkalemia*. Research advisor: Bruce Lambert, PhD

HONORS AND AWARDS

2003	Second class scholarship for academic excellence (top 10%)
2004	Second class scholarship for academic excellence (top 10%)
2005	First class scholarship for academic excellence (top 3%), Mary Kay Scholarship for Leadership
2007	Rho Chi Pharmacy Honor Society
2009 – 2011	Program for Excellence in Science Award, the American Association for the Advancement of Science

WORK EXPERIENCE

2007 – 2008	Department of Pharmacy Administration, UIC, Graduate Research Assistant. Chicago, IL
Summer 2009	Astellas Pharma., New Product Commercial Analysis Intern. Deerfield, IL
Summer 2010	Eli Lilly and Co., Global Health Outcomes Intern. Indianapolis, IN
2008 – 2011	UIC-Center for Education and Research on Therapeutics (**CERT**), funded by Agency for Healthcare Research and Quality (**AHRQ**), Research Specialist/Graduate Research Assistant. Chicago, IL

PROFESSIONAL SOCIETY MEMBERSHIPS

2007 – pres.	International Society for Pharmacoeconomics and Outcomes Research (**ISPOR**)
2009 – 2011	American Public Health Association
2009 – 2010	American Heart Association

PEER-REVIEWED PUBLICATIONS

- Silberstein SD, Marmura MJ, Shaw JW, **Yu SS**. Headache prophylaxis with BoNTA: patient characteristics. [Headache. 2009; 50(1): 63-70.]

- Shaw JW, Pickard AS, **Yu SS**, Chen SJ, Iannacchione VG, Johnson JA, Coons SJ. A median model for predicting United States population-based EQ-5D health state preferences. [Value in Health. 2009; 13(2): 278-288.]

- **Yu SS,** Galanter W, DiDomenico R, Borkowsky S, Schiff G, Lambert BL. Selection of drug-laboratory result pairs for an Inpatient Asynchronous Alert Program: Results of a Delphi Survey. Am J Health Syst Pharm. 2011 Mar 1; 68(5): 407-14.

- **Yu S,** Burge RT, Foster SA, Gelwicks S, Meadows ES. The impact of teriparatide adherence and persistence on fracture outcomes. Osteoporos Int. 2011; 23(3): 1103-1113

POSTERS AND PODIUM PRESENTATIONS BY SSY

- **Yu SS**, Shaw JW, Chen SJ, Iannacchione VG, Johnson JA, Coons SJ. A median model of US EQ-5D health state preferences. 24th Plenary Meeting of the EuroQol Group, Kijkduin, The Netherlands, September 13-14, 2007. (discussion paper)
- **Yu S**, Shaw JW, Crawford SY, Groo V. Impact of cardiovascular disease risk on the association between dietary supplement use and attempted weight loss in the US adult population. American Heart Association Scientific Sessions 2009, Orlando, FL, November 14-18, 2009. (poster presentation) [Abstract: Circulation. 2009; 120:S488.]
- **Yu SS**, Galanter WL, Lambert BL, Schiff GD, Borkowsky S. Consensus list of priority drug-lab linkages for an inpatient asynchronous alert program: results of a Delphi survey. American Society of Health-System Pharmacy 2009 Midyear Clinical Meeting, Las Vegas, NV, December 6-10, 2009.
- **Yu SS**, Lambert BL, Galanter W, Walton S. The Effect of Comorbility on Statin Compliance and Persistence. UIC College of Pharmacy Research Day 2010, Chicago, IL, February 26, 2010.
- **Yu S**, Shaw JW, Crawford SY, Groo V. Confounding Effect of Age in the Association of Cardiovascular Risk and Dietary Supplement Use among US Adults. International Society for Pharmacoeconomics and Outcomes Research 15th Annual International Meeting, Atlanta, GA, May 15-19, 2010. (Best Student Podium Presentation Award)
- **Yu S,** Galanter W, Lin FJ, Lambert B. Evaluation of Clinical Laboratory-pharmacy Linkage Decision Support in the use of Potassium Supplements. International Society for Pharmacoeconomics and Outcomes Research 16th Annual International Meeting, Baltimore, MD, May 21-25, 2011. (Podium presentation)
- **Yu S,** Foster S, Burge R, Anderson J, Gelwicks S, Meadows E. The Association between Teriparatide Persistence and Fracture Outcomes in a U.S. Claims Database. International Society for Pharmacoeconomics and Outcomes Research 16th Annual International Meeting, Baltimore, MD, May 21-25, 2011. (Poster presentation)
- **Yu S,** Galanter W, Lin FJ, Schiff G, Lambert B. Evaluation of Clinical Laboratory-pharmacy Linkage Decision Support in the use of Potassium Supplements. CERTs Monthly Scientific Conference Call, June 14th, 2011

CO-AUTHORED ABSTRACTS AND PRESENTATIONS

- Kaiser RS, Shaw JW, **Yu S**, Abbas MA. Does headache diagnosis moderate the performance of scales for measuring depression in adolescents. 49th Annual Scientific Meeting of the American Headache Society, Chicago, IL, June 7-10, 2007. (poster presentation) [Headache. 2007 May; 47(5): 807-808.]

- Abbas MA, Shaw JW, **Yu S**, Kaiser RS. Prevalence of comorbid depression in adolescents with headache and relationship to various types of headaches: a retrospective study. 49th Annual Scientific Meeting of the American Headache Society, Chicago, IL, June 7-10, 2007. (poster presentation) [Headache. 2007 May; 47(5): 809.]
- Shaw JW, Kaiser RS, **Yu SS**, Abbas MA. Criterion validity of the BDI-II and MMPI-A Depression scale in tertiary care adolescent headache patients. 13th Congress of the International Headache Society, Stockholm, Sweden, June 28-July 1, 2007. (poster presentation) [Cephalalgia. 2007 Jun; 27(6): 634.]
- Shaw JW, **Yu SS**, Chen SJ, Iannacchione VG, Johnson JA, Coons SJ. There's nothing "average" about these weights: development and testing of a median model of US EQ-5D health state preferences. 14th Annual Conference of the International Society for Quality of Life Research, Toronto, Canada, October 10-13, 2007. (poster presentation) [Quality of Life Research. 2007 Oct; 16(Suppl. 2): A-128.]
- Silberstein SD, Shaw JW, Marmura M, **Yu SS**. Program to Assess Headache Treatment Strategies (PATS): patient characteristics from a large observational study of botulinum toxin type A (BoNTA) prophylactic headache treatment. 60th Annual Meeting of the American Academy of Neurology, Chicago, IL April 12-19, 2008. (poster presentation) [Neurology. 2008; 70(11 Suppl. 1): A477, Abstract P08.194.]
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