

Improving Quality of Care in Acute Cardiology

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Improving Quality of Care in Acute Cardiology

Verbeteren van de kwaliteit van zorg in de acute cardiologie

Thesis

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Introduction

GENERAL INTRODUCTION

Acute cardiac care has changed dramatically over the past decennia. In coronary care and general intensive care units, information technology was introduced for arrhythmia monitoring and other signal processing (1,2). More recently, information technology has been applied to assist clinical decision making. **Chapter 1** provides a definition for clinical decision support systems (CDSS) in critical care and describes factors for successful implementation of such systems. Subsequent chapters present three groups of studies designed to improve patient care (**I**) using information technology to assist rapid diagnosis and treatment in patients with evolving myocardial infarction, (**II**) better managing the multitude of monitoring alarms and (**III**) improving glucose regulation in patients at an intensive cardiac care unit.

The first coronary care units were established to provide arrhythmia monitoring and treatment of life threatening arrhythmias in patients with acute myocardial infarction (AMI) (1,2). The introduction of thrombolytic therapy in the 1970's (3) and later primary percutaneous coronary intervention for the treatment of AMI (4,5) provided specific challenges for the organization of coronary care. Since delay in treatment is associated with worse outcome (6,7), an efficient and effective pre- and in-hospital clinical pathway is required for patients with chest pain. Information technology could assist in the decision making process for patients with chest pain and suspected myocardial infarction.

We present different strategies to improve the interpretation of the pre-hospital 12-lead electrocardiogram (ECG) as this is a key element in the triage of patients with chest pain. One approach is to leave the decision making to the pre-hospital caregiver. **Chapter 2** describes the ability of paramedics to diagnose ST-elevation AMI, and the influence of confounding electrocardiographic factors on their diagnosis. A different approach is to send the ECG to a cardiologist for analysis. **Chapter 3** describes the technical aspects of implementing a system for pre-hospital ECG transmission from the ambulance to a cardiologist. **Chapter 4** presents initial results and show examples of such system with regard to effectiveness in a subset of patients with chest pain.

Once a patient has arrived at the hospital, different approaches can be taken to minimize in-hospital delay to reperfusion therapy. In **chapter 5** the effectiveness of a set of hospital care improvement strategies was evaluated with regard to reducing delay to percutaneous coronary intervention.

Improvements in patient monitoring technology have transformed the intensive cardiac care unit into an environment rich in advanced technological devices. The need to monitor an increasing number of clinical parameters in complex patients leads to an increase in alerts generated by the monitoring devices. Most of these alerts are not related to

life-threatening events (8-10). Therefore, in part two of this thesis, we investigated several approaches to manage the multitude of monitoring alarms. **Chapter 6** describes the distribution of different types of patient monitoring alarms over time. To introduce interventions that can reduce frequency and improve relevance of alarms, a system was needed to collect and channel alarm data from different monitoring devices through a central gateway. **Chapter 7** describes such a system. Once such a system is in place, it provides a platform to improve the delivery of the alarms to the dedicated caregiver. The use of electronic portable devices for this purpose is described in **chapter 8**.

Part three touches a controversial issue: glucose regulation and outcome in critical illness. In a general intensive care setting a study done in Leuven showed a reduction in mortality when glucose was strictly regulated (11). Subsequent studies (12,13), however, could not confirm these observations. Strict glucose regulation was also studied in patients with acute coronary disease. An overview of these trials is given in **chapter 9**. We studied the association between admission glucose or average glucose levels and subsequent mortality in high risk patients admitted to an intensive cardiac care unit (**chapter 10**).

Many different protocols exist to regulate glucose through intravenous insulin administration. We expect that adherence to such protocols can be improved with information technology. **Chapters 11 and 12** describe the process of implementing a CDSS for glucose control in an intensive cardiac care unit. **Chapter 13** describes the effect of a CDSS for glucose control on compliance with the insulin protocol and achievement of glycemic targets. An important characteristic of a CDSS is its ability to generate data on protocol or guideline compliance, which in turn can be used to modify and improve the system. In **chapter 14** this process of using data acquired from the CDSS to make modifications to the protocol is described. Also, the effects of these evidence based modifications are investigated with regard to compliance with the insulin protocol and glucose levels.

Together, these three groups of studies reflect the ongoing process of improving patient care using dedicated information technology.

REFERENCES

1. JULIAN DG. Treatment of cardiac arrest in acute myocardial ischaemia and infarction. *Lancet*. 1961 Oct 14;2(7207):840-844.
2. KOUWENHOVEN WB, JUDE JR, KNICKERBOCKER GG. Closed-chest cardiac massage. *JAMA*. 1960 Jul 9;173:1064-1067.
3. Chazov El, Golikov AP. Use of streptodectase in acute myocardial infarct. *Kardiologija*. 1981 Dec;21(12):10-14.
4. Zijlstra F, de Boer MJ, Hoorntje JC, Reiffers S, Reiber JH, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N. Engl. J. Med*. 1993 Mar 11;328(10):680-684.
5. Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. *The Primary Angioplasty in Myocardial*

- Infarction Study Group. *N. Engl. J. Med.* 1993 Mar 11;328(10):673-679.
6. Bouten MJ, Simoons ML, Hartman JA, van Miltenburg AJ, van der Does E, Pool J. Prehospital thrombolysis with alteplase (rt-PA) in acute myocardial infarction. *Eur. Heart J.* 1992 Jul;13(7):925-931.
 7. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet.* 1996 Sep 21;348(9030):771-775.
 8. Siebig S, Kuhls S, Imhoff M, Gather U, Schölmerich J, Wrede CE. Intensive care unit alarms--how many do we need? *Crit. Care Med.* 2010 Feb;38(2):451-456.
 9. Blum JM, Tremper KK. Alarms in the intensive care unit: Too much of a good thing is dangerous: Is it time to add some intelligence to alarms?*. *Critical Care Medicine.* 2010 2;38(2):702-703.
 10. Chambrin MC, Ravoux P, Calvelo-Aros D, Jaborska A, Chopin C, Boniface B. Multicentric study of monitoring alarms in the adult intensive care unit (ICU): a descriptive analysis. *Intensive Care Med.* 1999 Dec;25(12):1360-1366.
 11. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in the critically ill patients. *N. Engl. J. Med.* 2001 Nov 8;345(19):1359-1367.
 12. Wiener RS, Wiener DC, Larson RJ. Benefits and Risks of Tight Glucose Control in Critically Ill Adults: A Meta-analysis. *JAMA.* 2008 Aug 27;300(8):933-944.
 13. The NICE-SUGAR Study Investigators. Intensive versus Conventional Glucose Control in Critically Ill Patients. *N Engl J Med.* 2009 Mar 26;360(13):1283-1297.

Chapter 1

Clinical decision support systems:
important tools when appropriately used

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Jan Hazelzet

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Clinical decision support systems (CDSS) may be defined as “information systems that aid providers in various aspects of clinical decision-making” (1). Practically speaking, a CDSS selects relevant, patient specific data and presents this so the caregiver can make a “better” decision. The decision may be diagnostic or treatment directed, but the decision advice presentation to the caregiver is of key importance: when improperly integrated into the clinical workflow, implementation of a CDSS may affect quality of care adversely.

The intensive care unit (ICU) is a complex environment where many important diagnostic and treatment decisions are made every day. The decisions are based on several types of data elements coming from medical devices, laboratory results, assessments documented in a clinical information system, but also should take into account protocol and guideline-based recommendations. However, these protocols may change frequently and can be complex. Also, the availability may differ: sometimes protocols and guidelines exist on article, in various digital formats, and stored centrally on the hospital network or locally on a personal computers.

On the ICU, there is little margin for error, and decisions need to be made with minimal delay. Sicker patients are more often harmed by such errors (2), and especially in the pediatric ICU, where patients from 2 kg to 80 kg are treated, the risk for errors is further increased. This augments the need for tailoring information technology systems and places specific demands on commercially available systems (3).

For these reasons, workflow and decision support by electronic information systems can be helpful in the ICU. Ideally these systems should help us in improving care by making it more safe, efficacious, and efficient. This means real diagnostic and treatment decision support at the bedside, in an appropriate form and at the right moment. At this moment, there is no overview of the present possibilities and guide to successful implementation, which might lead to individual and non-integrated choices.

A review of Mack et al (1) fulfils a challenging task of providing an overview of CDSS applications for the pediatric ICU. An extensive literature review was performed resulting in a general historic overview, a focus on several systems, and a discussion on successful implementation.

The review includes a practical guide regarding personal digital assistant, web based and stand-alone CDSS systems, with references and links to the Web sites. CDSS integration with electronic health records are described in more detail using the implementation of a computerized physician medication order entry system to illustrate the importance and difficulty of the implementation process.

Three studies are described in more detail: a study presenting a higher mortality after implementing a CDSS for medication entry (4), and two studies that did not result in a negative effect on patient care after implementation of CDSS (5, 6). As the authors conclude, CDSS implementation is a complex process where evaluation should be done to analyze the utilization of the CDSS, the adherence to the CDSS alerts, and the effect of

CDSS on clinical outcomes. A key issue regarding evaluation is mentioned as well; it will rarely be possible to find a similar hospital with similar healthcare systems to function as a control group. Thus, ideally, implementation of a CDSS should be done in a carefully designed study setting, starting with prospective evaluation of the setting before implementation, followed by a randomization within the institution to CDSS or current care. Analysis of the data makes it possible to study the clinical effectiveness of CDSS while accounting for effects of other process changes on patient outcome (7). Furthermore, evaluation information gathered by the CDSS can be used to improve guidelines. The administration of the clinical rules in a large unit or especially in a hospital is an important item. This is important to prevent overuse or incorrect use in some environments (8). In this way, improving decision rules is a continuous process.

What are the keys to successful implementation of a CDSS? A more general review (9) analyzed 70 randomized controlled CDSS trials and identified four features that significantly improved clinical practice: of 32 systems possessing all four features, 30 significantly improved clinical practice (94%). The authors cite these findings, and other factors of importance, which are summarized in Table 1.

Table 1: Consideration points when choosing a clinical decision support system

Design and implementation
Integration with workflow
Need for user training and culture change
Minimize complexity of implementation process
Implement one new system at a time
Aquisition of data
Automated by integration with the hospital information and charting system
Requesting additional information only when absolutely necessary
Presentation of alert
Automated alerting as soon as data becomes available
Alert is accompanied by a evidence based recommendation as default, but also provides alternatives
Selectively targeted to the environment or situation
Intrusiveness based on level of severity
Evaluation
Evaluate system utilization, but also clinical variables
Require a reason for not following advice
Potential pitfalls
Overreliance of users on technology
Ignoring important alerts due to alert fatigue
Incorrect advice due to accidental selection of wrong patient
Incorrect entry of (verbal) orders

From: Mack EA, Wheeler DS, Embi PJ: Clinical decision support systems in pediatric intensive care. *Pediatr Crit Care Med* 2009; 10:23–28

Further areas for CDSS application are improving ICU safety as well as supporting the implementation of evidence-based guidelines (10). Some examples are small tidal volumes and inappropriate transfusions (11), as well as the reduction in use of broad-spectrum antibiotics (12). Currently, there are few hospitals with fully electronic critical care systems, and these are only partly linked to the hospital systems (13). To fully benefit from CDSS, intensive care clinical information systems need to integrate with the hospital and national clinical record initiatives.

Any CDSS application needs to be designed to fit into the clinical workflow, where careful evaluation not only on the utilization, but also on clinical outcomes is necessary. Future CDSS will improve adherence to, but also aid developments of new, improved guidelines: CDSS can play a key role in evidence-based medicine in the intensive care setting.

REFERENCES

1. Mack EA, Wheeler DS, Embi PJ: Clinical decision support systems the pediatric intensive care. *Pediatr Crit Care Med* 2009; 10:23–28
2. Kozer E, Berkovitch M, Koren G: Medication errors in children. *Pediatr Clin North Am* 2006; 53:1155–1168
3. Giannone G: Computer-supported weightbased drug infusion concentrations in the neonatal intensive care unit. *Comput Inform Nurs* 2005; 23:100–105
4. Han YY, Carcillo JA, Venkataraman ST, et al: Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system. *Pediatrics* 2005; 116:1506–1512
5. Del Beccaro MA, Jeffries HE, Eisenberg MA, et al: Computerized provider order entry implementation: No association with increased mortality rates in an intensive care unit. *Pediatrics* 2006; 118:290–295
6. Mullett CJ, Evans RS, Christenson JC, et al: Development and impact of a computerized pediatric antiinfective decision support program. *Pediatrics* 2001; 108:E75
7. Adhikari N, Lapinsky SE: Medical informatics in the intensive care unit: Overview of technology assessment. *J Crit Care* 2003; 18:41–47
8. van der Sijs H, Aarts J, van Gelder T, et al: Turning off frequently overridden drug alerts: Limited opportunities for doing it safely. *J Am Med Inform Assoc* 2008; 15:439–448
9. Kawamoto K, Houlihan CA, Balas EA, et al: Improving clinical practice using clinical decision support systems: A systematic review of trials to identify features critical to success. *BMJ* 2005; 330:765
10. Sucher JF, Moore FA, Todd SR, et al: Computerized clinical decision support: A technology to implement and validate evidence based guidelines. *J Trauma* 2008; 64:520–537
11. Yilmaz M, Keegan MT, Iscimen R, et al: Toward the prevention of acute lung injury: Protocol guided limitation of large tidal volume ventilation and inappropriate transfusion. *Crit Care Med* 2007; 35:1660–1666; quiz 1667
12. Thursky KA, Buising KL, Bak N, et al: Reduction of broad-spectrum antibiotic use with computerized decision support in an intensive care unit. *Int J Qual Health Care* 2006; 18:224–231
13. Tackley R: Integrating anaesthesia and intensive care into the National Care Record. *Br J Anaesth* 2006; 97:69–76

Part I

Decision making in acute cardiac care

Chapter 2

Comparison of the ability of paramedics with that of cardiologists in diagnosing ST-segment elevation acute myocardial infarction in patients with acute chest pain

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INTRODUCTION

Both percutaneous coronary intervention and intravenous thrombolysis have been shown to be most effective when given within the first 2 hours after the onset of symptoms (1-4). As further time elapses, the benefits of reperfusion therapy decline. In an effort to reduce time from symptom onset to treatment, emergency medical systems have been implementing cellular transmission of electrocardiograms (ECGs) to receiving stations in hospitals since 1987 (5,6). However, electrocardiographic transmission directly to a consulting cardiologist's wireless hand-held device (mobile phone or pocket computer) with web-browsing capabilities has only recently become an option (7). To limit the workload associated with this on-line acute consulting function, paramedics must be able to interpret as well as acquire ECGs. The purpose of the present study was to determine the paramedics' true-positive rate of ST elevation acute myocardial infarction (AMI) diagnosis, and to assess the influence of confounding electrocardiographic factors on the paramedics' diagnosis.

METHODS

One hundred thirty-two consecutive patients from the Timely Intervention in Myocardial Emergency 2 trial were reviewed and analyzed retrospectively. Those included in this study were diagnosed with ST elevation AMI by paramedics based on their prehospital ECG, and transported by Guilford County Emergency Medical Services to Moses Cones Memorial Hospital during a 1-year period, from 2000 to 2001. During this time period, approximately 1,200 patients had a 12-lead ECG recorded by paramedics from this emergency medical service (personal communication). Patients were excluded when the following data were incomplete: (1) prehospital 12-lead ECG, (2) hospital admission ECG, (3) final hospital ECG, and (4) hospital data form. Only 6 patients were excluded because of an incomplete prehospital ECG, whereas 5 were excluded because of missing hospital data. The final study group consisted of 121 patients.

The hospital is a 650-bed regional medical center located in Guilford County, North Carolina, and performs percutaneous coronary intervention on a 24-hour basis as the reperfusion therapy of choice in patients with ST elevation AMI. During the 8 years that Guilford County Emergency Medical Services has been acquiring 12-lead ECGs in ambulances, paramedics have been required to attend initial and continuing education courses on cardiac care, including cardiac pathophysiology and acquisition, and interpretation of the 12-lead ECG. Paramedics must pass a written examination and demonstrate proficiency in acquisition and interpretation at least once a year.

Paramedics completed an emergency medical services case report form for each patient they considered to be eligible based on ST-segment elevation of ≥ 1 mm in ≥ 2

contiguous leads present on the standard 12-lead prehospital ECG (8). There was an immediate computer interpretation available to paramedics, who then confirmed or altered the interpretation. The case report form included demographic and clinical data, as well as times of symptom onset, emergency medical services call, prehospital ECG, and arrival at the emergency department. The hospital data form included type of procedure (percutaneous coronary intervention, coronary angiography, or neither), time of arrival to the catheterization laboratory, treatment times, and procedural and hospital outcomes. Data processing was performed at the Duke University ECG Core Laboratory. Digitized prehospital ECGs were recorded during transportation of patients to the hospital and later transmitted electronically to the ECG Core Laboratory and printed on an electrocardiograph machine. If digital data were not available, paper electrocardiographic copies were attached to the emergency medical services case report form and sent to the ECG Core Laboratory. ECGs obtained at hospital admission and before hospital discharge were transmitted directly to an electrocardiograph machine in the ECG Core Laboratory via an analog telephone line.

An experienced cardiologist blinded to all other clinical data analyzed all 12-lead ECGs. This clinician served as a surrogate for the local on-call cardiologist in the clinical situation in which the ECG would be transmitted directly from the ambulance to the cardiologist's handheld device. The study coordinator ensured that the ECG analyst was blinded to all other data, and that the data analysis occurred in the following sequence: (1) Based on the prehospital ECG, it was determined whether the patient met the criteria for ST elevation AMI (8). (2) the presence of confounding factors (left/right bundle branch block, left anterior/posterior fascicular block, left/right ventricular hypertrophy, ventricular rhythm, Wolff-Parkinson-White syndrome, poor quality [unstable baseline and lead reversal], or prior myocardial infarction [defined by the presence of abnormal Q waves (9) in leads without ST elevation]) was determined on the prehospital ECG. (3) A final electrocardiographic diagnosis based on evolution from the prehospital ECG to the predischarge ECG was performed. ST-segment resolution, Q-wave development, R- and S-wave amplitude attenuation, and inversion of T waves were considered evidence of myocardial infarction evolution (9-12).

The presence of an occlusive thrombus of a major coronary artery was determined by emergency coronary angiographic results. Catheterization was considered positive when the initial coronary obstruction (stenosis or thrombus) was $\geq 95\%$, and the Thrombolysis In Myocardial Infarction flow designation increased from 0 or 1 to either 2 or 3; otherwise it was considered negative. Patients without acute coronary angiography were considered not to have a thrombotic occlusion, unless they had serial electrocardiographic evolution as previously defined, accompanied by transient elevation in creatine kinase-MB.

The chi-square statistic was used to compare the cardiologist's and paramedics' true-positive rates of ST elevation AMI diagnosis, both overall and in the presence of electrocardiographic confounding factors.

RESULTS

Mean \pm SD age for the 121 study patients was 65 ± 16 years. The study included 41 women (34%) and 93 Caucasians (77%). Other baseline characteristics were systemic hypertension in 48 patients (40%), diabetes mellitus in 21 (17%), history of bleeding problems in 1 (1%), prior myocardial infarction in 21 (17%), prior coronary bypass in 19 (16%), prior percutaneous coronary intervention (<6 months) in 5 (4%), current smoker in 39 (32%), and congestive heart failure/acute pulmonary edema in 8 patients (7%).

The paramedics' diagnosis of ST elevation AMI was confirmed in 55 patients (45.5%) by acute angiography. In an additional 4 patients (3.5%) who did not undergo angiography due to high-risk assessment or other causes, the diagnosis was confirmed clinically by typical electrocardiographic changes in evolving ST elevation AMI accompanied by transient elevation of creatine kinase-MB. Thus, the paramedics' true-positive rate was 49% ($n = 59$). The paramedics' decision was not confirmed in the 23 patients (19%) with no thrombus at angiography, and in the 38 (31%) who did not undergo coronary angiography because the attending cardiologist judged them not to have an evolving ST elevation AMI. One patient had an indeterminate catheterization because the initial infarct-related artery stenosis was 70%. The false-positive rate by paramedics was 51% ($n = 62$).

The presence and type of confounders, as well as the percentage of patients with confirmed ST elevation AMI by confounder type, are listed in Table 1. The paramedics' true-positive rate of ST elevation AMI diagnosis was 36% in the group with confounders versus 60% in the group without confounding factors ($p = 0.010$). In comparison, the cardiologist's overall true-positive rate was 88%, and thus significantly higher than that of the paramedics ($p < 0.0001$). Unlike the paramedics, the cardiologist's true-positive rate of ST elevation AMI was similar in groups with and without electrocardiographic confounding factors (89% vs 87%) ($p = 0.71$).

Table 1: Presence and Type of Confounding Factors, and the Percentage of Patients With Confirmed ST Elevation AMI by Type of Confounding Factor ($n = 121$)

		ST Elevation AMI (true positive)
Electrocardiographic confounder	56 (46%)	36%
Prior AMI	15 (12%)	20%
Poor quality ECG	13 (11%)	67%
Right bundle branch block	9 (7%)	44%
Left anterior fascicular block	8 (7%)	38%
Left bundle branch block	6 (5%)	17%
Left ventricular hypertrophy	4 (3%)	25%
Pacemaker	1 (1%)	0%

The incidence of poor quality ECGs recorded by the paramedics was calculated to determine the paramedics' performance in electrocardiographic acquisition. In 13 of 124 patients (10.5%), the ECGs were characterized as poor quality (unstable baseline or lead reversal). In 6 of 11 patients excluded from this study, the cause was an incomplete baseline ECG recorded by paramedics.

DISCUSSION

Prehospital electrocardiographic acquisition and transmission is essential to further reduce time from symptom onset to treatment in patients with ST elevation AMI. The system of electrocardiographic transmission directly to the on-call cardiologist's wireless hand-held device provides parallel transmission to the emergency department and the cardiologist. This technology will be tested in the Timely Intervention in Myocardial Emergency 2 trial in Guilford County, North Carolina. It is the hypothesis of this study that primary percutaneous coronary intervention will be more rapidly initiated when the responsible cardiologist has support for the reperfusion therapy decision via immediate access to patient data, including a standard 12-lead ECG. This study is the first to systematically examine the ability of paramedics to acquire and interpret ECGs to enable accurate diagnosis of patients with ST elevation AMI in preparation for systematically transmission directly to a cardiologist.

The paramedics' true-positive rate of ST elevation AMI diagnosis (verified by angiography and subsequent electrocardiographic evolution as the "gold standard") in patients with acute chest pain was good in those presenting without confounding factors, but was diminished when the ECG was abnormal due to pathologic conditions such as prior myocardial infarction, left bundle branch block, or left ventricular hypertrophy. These results for paramedics were in direct contrast to those for the cardiologist, whose level of performance was higher and was not affected by confounders. The incidence of poor quality ECGs in the study population was acceptable at 10.5%.

Paramedics diagnosed over half of patients as having ST elevation AMI, when in fact they did not. One reason for this may be that the paramedics were concerned about missing patients with this condition. The number of false-positive diagnoses may also have been increased due to the problem of differentiating ST elevation AMI from other electrocardiographic abnormalities that result in ST-segment elevation (13-15). Zhou et al (16) developed an algorithm to distinguish ST elevation AMI from benign early repolarization or acute pericarditis. Employment of such an algorithm may assist paramedics in differentiating among these 3 conditions. Left bundle branch block is 1 of the factors that causes difficulty when diagnosing ST elevation AMI, because it conceals electrocardiographic changes in ST elevation AMI. Further training of paramedics to include more sophisticated algorithms, such as those available for concomitant left bundle branch block (17), may be

Acute of value in the future. Thus, enhancement of the paramedics' skills and knowledge that focus on these and other 12-lead electrocardiographic abnormalities is essential to reduce the number of patients with false-positive results observed in this study.

CONCLUSION

This study concludes that paramedics' true-positive rate of ST elevation AMI diagnosis is high in patients presenting without confounding factors, but decreases when the ECG has confounding factors. This is in contrast to an experienced cardiologist whose true-positive rate was high and not affected by confounding factors. The results demonstrate that before implementation of electrocardiographic transmission directly to a cardiologist's handheld device, there is a need to provide education and training to paramedics responsible for acquiring and interpreting prehospital ECGs, with special emphasis on confounders.

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REFERENCES

1. Boersma E, Maas ACP, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: appraisal of the golden hour. *Lancet* 1996;348:771–775.
2. Rawls JM. Quantification of the benefit of earlier thrombolytic therapy: five-year results of the grampian region early anistreplase trial (GREAT). *J Am Coll Cardiol* 1997;30:1181–1186.
3. Milavetz JJ, Giebel DW, Christian TS, Schwartz RS, Holmes DR, Gibbons RJ. Time to therapy and salvage in myocardial infarction. *J Am Coll Cardiol* 1998;31:1246–1251.
4. Brodie BR, Stuckey TD, Wall TC, Kissling G, Hansen CJ, Muncy DB, Weintraub RA, Kelly TA. Importance of time to reperfusion for 30-day and late survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 1998;32:1312–1319.
5. Grim P, Feldman T, Martin M, Donovan R, Nevins V, Childers RW. Cellular telephone transmission of 12-lead electrocardiograms from ambulance to hospital. *Am J Cardiol* 1987;60:715–720.
6. Wall TC, Albright J, Livingston B, Isley L, Young D, Nanny M, Jacobowitz S, Maynard C, Mayer N, Pierce K, et al. Prehospital ECG transmission speeds reperfusion for patients with acute myocardial infarction. *NC Med J* 2000;61: 104–107.
7. Pettis KS, Kwong M, Wagner GS. Prehospital diagnosis and management of patients with acute myocardial infarction using remote transmission of electrocardiograms to palmtop computers. In: Clements IP, ed. *The Electrocardiogram in Acute Myocardial Infarction*. Armonk, New York: Futura, 1998:223–234.
8. Alpert JS, Thygesen K. Myocardial infarction redefined: a consensus document of the joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. *Eur Heart J* 2000;21: 1502–1513.
9. Selvester RH, Wagner GS, Hindman NB. The Selvester QRS scoring system for estimating myocardial infarct

- size: the development and application of the system. *Arch Intern Med* 1985;145:1877–1881.
10. Smith FM. The ligation of coronary arteries with electrocardiographic study. *Arch Intern Med* 1918;22:8–27.
 11. Essen RV, Merx W, Effert S. Spontaneous course of ST-segment elevation in acute myocardial infarction. *Circulation* 1979;59:105–112.
 12. GUSTO IIa Investigators. Randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. The global use of strategies to open occluded coronary arteries (GUSTO) IIa investigators. *Circulation* 1994;90:1631–1637.
 13. Mehta M, Jain AC, Mehta A. Early repolarization. *Clin Cardiol* 1999;22:59–65.
 14. Teh BS, Walsh J, Bell AJ, Walker SJ, Kilpatrick D. Electrical current paths in acute pericarditis. *J Electrocardiol* 1993;26:291–300.
 15. Spodick DH. Differential characteristics of the electrocardiogram in early repolarization and acute pericarditis. *N Engl J Med* 1976;295:523–526.
 16. Zhou S, Helfenbein E, Lindauer J, Clifton J, Selvester RH, Wagner GS. Classification of ST elevation acute myocardial infarction, acute pericarditis, and benign early repolarization. *J Electrocardiol* 2000;33(suppl):251.
 17. Sgarbossa EB, Pinski SL, Barbagelata A, Underwood DA, Gates KB, Topol EJ, Califf RM, Wagner GS, for the GUSTO-I Investigators. Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundlebranch block. *N Engl J Med* 1996;334:481–487.

Chapter 3

The future of STEMI response: Implementing field-to-cardiologist ECG transmission to accelerate reperfusion in acute MI

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INTRODUCTION

Medic 6 arrives at the home of a 68-year-old male with chest pain. After conducting a complete assessment, obtaining a 12-lead electrocardiogram (ECG) and starting initial interventions, the crew sends the 12-lead directly from their monitor to the personal digital assistant (PDA) of a cardiologist. The physician hears the device's alert tone, checks the PDA and evaluates the ECG in real time.

The cardiologist evaluates the patient's ECG to determine if it meets criteria for emergency reperfusion therapy in the facility's cardiac catheterization (cath) lab. It does, so he advises the crew to bypass the emergency department (ED) and proceed directly to the cath lab where he and his team will meet the patient.

The crew acknowledges the cardiologist's orders and then notifies the ED. The patient arrives at the hospital 12 minutes later and within another seven minutes is under the care of the specialized catheterization team.

Sound far-fetched? It's not. Technology has begun to make this scenario happen in emergency medical service (EMS) systems throughout the world. This article describes the protocol used to study this clinically important and innovative technology.

BACKGROUND

An estimated 2 million annual hospital discharges in the United States are for acute coronary syndromes, and one-third of these patients have ST-elevation myocardial infarction (STEMI) (1). The underlying cause of STEMI is typically an acute occlusion of a coronary artery (e.g., thrombosis).

The rapid identification of STEMI should be of highest priority to EMS crews because reperfusion treatments (e.g., thrombolytic medications or mechanical intervention in the cath lab) can save cardiac muscle and potentially even the patient's life if treatment is administered rapidly (2-5). To reduce the time from onset of acute thrombosis to reperfusion therapy, clinicians have employed numerous strategies, including patient educational initiatives (6-8), specific acute myocardial infarction (MI) protocol development for EDs (9-15), prehospital ECG transmission from EMS vehicles to EDs (16-19) and prehospital thrombolysis (20-25).

Cellular transmission of ECGs to receiving hospitals has been in use by EMS systems since 1987 (26). In the TIME 1 (Timely Intervention in Myocardial Emergency 1) trial in Guilford County, N.C., Wall et al documented a 27% time reduction (109 to 80 minutes) from hospital arrival to percutaneous coronary intervention (PCI) by implementing prehospital ECG transmission to the ED (19). However, a follow-up study revealed that the initial decrease in door-to-balloon time was not sustained over a 10-year period (27).

These results stimulated the discussion of whether door-to balloon times could be

consistently reduced for patients with clearly abnormal ECGs by increasing direct communication between paramedics and cardiologists. Such a system would involve paramedics evaluating 12-lead ECGs for ST-elevation and directly contacting the cardiologist when STEMI was present. [Note: A study found that the true-positive rate of STEMI diagnosis by paramedics is high in patients presenting without confounding factors, e.g., prior myocardial infarction (MI), poor-quality ECG, bundle branch block, left ventricular hypertrophy and pacemaker, but decreases when the ECG has confounding factors (28)]

ECG transmission directly from a prehospital ECG monitor to a handheld digital device has only recently become an option (29). This system can now provide parallel ECG transmission to the ED and an on-call cardiologist for patients with both symptoms and ST-segment changes that most strongly suggest an MI.

Testing of this technology has been performed in both Europe and the United States (30,31). The hypothesis of these studies is that the time to reperfusion therapy will be reduced when the assigned cardiologist has immediate access to a 12-lead ECG and other patient data directly from paramedics in the field. It's further hypothesized that earlier treatment will result in increased myocardial salvage as estimated by previously validated ECG scoring techniques described below (32-35).

Technical aspects

In the studies referenced, paramedics obtain a 12-lead ECG for patients experiencing symptoms suggestive of acute coronary syndrome. If a probable STEMI is indicated by at least 1 mm ST elevation in two or more contiguous leads, the ECG is transmitted from the ambulance to a central computer at the EMS headquarters or a hospital, using a cellular connection or digital wireless network (36). The ECG can be transmitted to a fax machine at the ED, a receiving station or a PDA. Systems with a receiving station can forward the ECG to a cath lab or other location.

Notification can also be sent to an on-call cardiologist's PDA. The small, handheld device alerts the physician of an incoming ECG. Using proprietary software, the cardiologist can download the ECG from the central computer and view it on the PDA screen. The software provides a view of the six limb leads, the six precordial leads and a more detailed zoom view of each individual lead. If the cellular connection to the PDA fails, the ECG is faxed to the hospital ED. The fax system is maintained as a back-up to the electronic transfer system. In addition, the ECGs are stored on the central computer, which facilitates their use for computing the predicted final MI size.

RESULTS

The method described was developed by investigators at Guilford County (N.C.) and Duke Clinical Research Institute in response to an absence of sustained reduction in time to

Acute reperfusion for STEMI patients (27). This ECG transfer method has been implemented in TIME studies in both Copenhagen, Denmark (TIME-C), and Cabarrus County, N.C. (TIME-NE), and is now the basis for multi-center TIME studies of two commercial prehospital ECG manufacturers (Figure 1) (30,37).

In addition, a study in Durham, N.C. (TIME-HL) has shown a significant decrease in door-to-balloon time when paramedics called the coronary care unit directly to activate the cath lab using a dedicated “hotline” (38). This intervention did not involve ECG transmission and relied solely on paramedic recognition of STEMI.

Figure 1: Evolution of the Timely Intervention in Myocardial Emergency (TIME) Studies

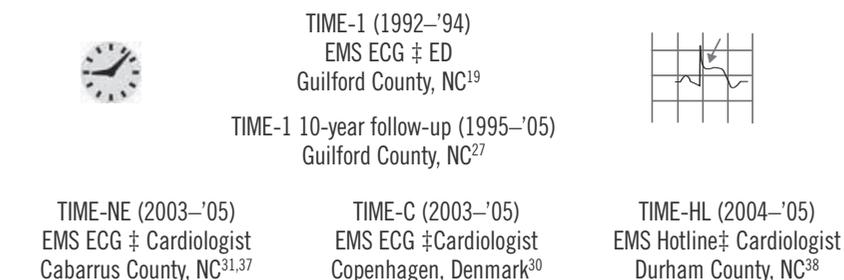


FIGURE LEGEND

TIME = Timely Intervention in Myocardial Emergency
 TIME-NE = Study at NorthEast Medical Center, Cabarrus County, NC
 TIME-C = Study in Copenhagen, Denmark
 TIME-HL = Study of a EMS-to-Cardiologist “Hotline” system in Durham, NC
 TIME-MC-1 = Multi-Center study at 12 sites
 TIME-MC-2 = Multi-Center study at 3 sites

The ideal environment for implementation

A community interested in implementing this technology must have a well-organized EMS system and hospital health system that provides primary coronary intervention and/or intravenous thrombolytic therapy on a 24-hour basis. Both EMS and the health system must have resources for collecting patient data into a computerized database. A relationship must be established with a study coordination center capable of designing the ECG transfer protocol, managing the data and determining the study outcomes. The cellular network must support messaging/paging services, as well as data and voice transmission services.

EMS involvement: Paramedics involved in remote transmission programs must be well-educated in the interpretation, recording and transmission of 12-lead ECGs, as well as in the advanced patient treatment associated with cardiac chest pain (28). The ambulances must be equipped to transmit the ECG via cellular or wireless technology.

An EMS research coordinator should be appointed to ensure the education of the paramedics and be responsible for testing, introducing, and maintaining the necessary tech-

nology. The coordinator would be responsible for monitoring and ensuring the correct functioning of the ECG transmission system and EMS data collection after the technology has been implemented.

Participating hospital involvement: Participating hospitals must provide reperfusion therapy on a 24-hour basis using thrombolytic therapy or PCI. Protocols must be established regarding the responsibilities of the paramedics, ED physicians and cardiologists. A research coordinator within the hospital must be appointed and given responsibility for obtaining data on patients with reperfusion therapy.

Study coordination center: A study coordination center should oversee the study progress, determining the requirements of each of the participants before the technology can be implemented in the community. The center must be experienced in coordinating clinical research studies and the testing of new technologies, and have facilities to maintain and analyze patient data in a study database and experts to analyze the ECGs.

A study coordinator establishes a system for data collection and analysis from the different sources and for direct communication between the participants. The coordinator appoints a Data Safety and Monitoring Board (DSMB) to approve the study design and monitor patient safety (39).

Communications flow

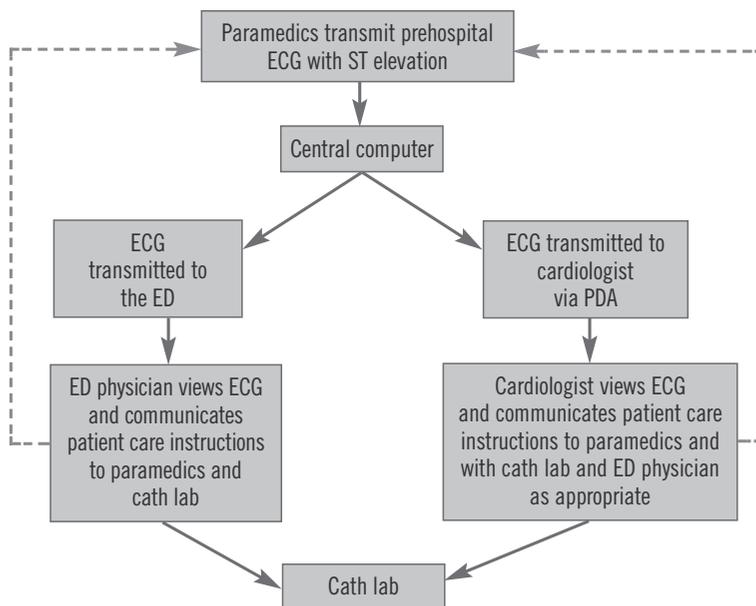
In our system, paramedics transmit an ECG for patients meeting STEMI criteria to a cardiologist's handheld digital device on a 24-hour basis. The cardiologist receives and views the ECG, and contacts the paramedic by phone. Assuming primary medical control, the cardiologist decides what emergency treatment is indicated and discusses the plan with the paramedic.

The paramedic then establishes contact with the ED charge nurse, providing information regarding the cardiologist's decision of treatment and transport site. Depending on local EMS capability and treatment protocols, the paramedic initiates field thrombolytics, transports the patient directly to the cath laboratory for PCI or transports the patient to the hospital ED, either for thrombolytic therapy or to hold until the cath lab is ready (Figure 2).

A protocol is followed for the patient to bypass the ED when the cath lab is operational, and a shortened admission protocol is followed when it's not operational so the patient can be transported to the cath lab as soon as it's available. If the patient will be transported directly to the cath lab, the cardiologist will notify the cath lab nurse directly. The cardiologist then meets the patient at the arrival site—the ED or the cath lab.

Data collection & analysis

To safely introduce this technology and monitor the ongoing study, it is essential to have a well-functioning data collection system. The study coordination center gathers the in-

Figure 2: Prehospital ECG Transmission and Communication Protocol

formation (Figure 3). Reports from these computerized databases provide information on patient flow and study progress. This database can then be queried for quality control and outcome research.

An ECG analyst calculates myocardial salvage by analyzing and comparing the transmitted and hospital discharge recordings (32,33,40-42). Automated ECG analysis programs facilitate this process by providing the required digital measurements.

The analysis includes demographic data, medical history, presenting patient characteristics, diagnosis and procedure utilization, delay and treatment time intervals, and hospital outcomes. Thus, patients with and without ECGs transmitted to the cardiologist can be compared.

LESSONS LEARNED

Before making the decision to implement this technology, control data on current time to treatment and transportation should be collected from the community regarding the patient population. In addition, the paramedics should be sufficiently trained in 12-lead ECG acquisition and diagnosing STEMI.

Technology: There are various methods of transmitting the ECG to a cellular device; there are also different types of devices. When making a choice between the technology options one should consider the availability, dependability (especially software reliability)

Figure 3: Key Data Elements to be Recorded

Technical & Procedural Data to Monitor Reliability	<p>From EMS/paramedic:</p> <ul style="list-style-type: none"> • Time of prehospital ECG transmission • Transmission information • Communication with cardiologist and ED <p>From cardiologist carrying receiving device:</p> <ul style="list-style-type: none"> • Notification of ECG received • Ability to view ECG • Treatment decision • Communication with paramedic and cath lab <p>From ECG recorder:</p> <ul style="list-style-type: none"> • Prehospital ECG
Information from Paramedics	<p>Dates & times of:</p> <ul style="list-style-type: none"> • Symptom onset • EMS arrival on scene • ECG recording • Hospital arrival <p>Patient baseline characteristics</p> <ul style="list-style-type: none"> • Date of birth, sex, race, etc. <p>Clinical data</p> <ul style="list-style-type: none"> • Chest pain characteristics • Risk factors • Medical history • Success of transmission • Communication and treatment decision
Patient Care Information from Hospital	<p>Dates and times of:</p> <ul style="list-style-type: none"> • Hospital admission (arrival at ED, arrival at cath lab) • Treatment (administration of thrombolytics or start of PCI) • Hospital discharge <p>Patient baseline characteristics (for matching with EMS data)</p> <p>Clinical data:</p> <ul style="list-style-type: none"> • Pre-treatment assessment • Treatment • Post-treatment assessment • Complications and survival

and capability of the cellular devices.

Transmission methods: To view a transmitted ECG on a cellular device as an electronic file requires specially designed software. Commercially available software and technology can also fax the ECG via a cellular device, although the quality of the ECG when displayed on the device needs to be verified (43,44).

Factors that should be evaluated are the image resolution, size and the number of leads that can be displayed on the cellular device at one time. The current technology is capable of displaying and transmitting ECGs but often has too many software issues to be sufficiently dependable.

Data entry & collection: Data should be entered as it becomes available, and appropriate edit checks should be applied. Separate databases can be used to analyze the ECGs and to

Acute track the transmissions. Establishing a central database that stores all patient data appears to be the most efficient setup. Because the number of study patients at a single site is limited, standardization of the data elements would be valuable for facilitating multi-center data analysis, providing stronger results.

Communication: The number of participating sites and organizations involved necessitates a structured feedback plan. Feedback from weekly visits of the study coordinator to the study sites and regular conference calls should be presented to all study participants in a newsletter.

An institutional review board (IRB) should monitor the study results and, if called for, terminate the study. A list of responsibilities for solving specific problems should also be established, and the study coordinator should refer to this list to gather information and set up conference calls to resolve any issues.

CONCLUSION

Based on our results, we recommend the implementation of this system be done in three phases:

Phase one: After developing an initial plan, the technology to be used is chosen and, if necessary, clinically tested. This applies to the treatment possibilities as well. Existing data from the community is evaluated.

Phase two: The communication lines and protocols are finalized and tested together with the technology. At the same time, data collection is started. Patient safety is ensured via an established backup system and a Data Safety and Monitoring Board that approves the study protocol. Final adjustments, based on testing results, are made to the technology and protocols.

Phase three: The technology is applied, allowing the cardiologists to make prehospital treatment decisions. The IRB monitors patient safety and study progress. The data are analyzed and compared with other communities.

Implementing this advanced technology requires a long-term commitment from all participants. Technology will always be changing, so clear communication protocols must form a framework for introduction of newer technologies.

REFERENCES

1. Antman EM, Anbe DT, Armstrong PW, et al: "ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 guidelines for the management of patients with acute myocardial infarction)." *Circulation*. 110:e82–292, 2004
2. Keeley EC, Boura JA, Grines CL: "Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomized trials." *Lancet*. 361:13–20. 2003.
3. Newby LK, Rutsch WR, Califf RM, et al: "Time from symptom onset to treatment and outcomes after throm-

- bolytic therapy. GUSTO-1 Investigators." *Journal of American College of Cardiology*. 27(7):1646–1655, 1996.
4. De Luca G, Suryapranata H, Ottervanger JP, Antman E: "Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts." *Circulation*. 109:1223–1225, 2004.
 5. Brodie BR, Hansen C, Stuckey TD, et al: "Door-to-balloon time with primary percutaneous coronary intervention for acute myocardial infarction impacts late cardiac mortality in high-risk patients and patients presenting early after the onset of symptoms." *Journal of American College of Cardiology*. 47(2):289–295, 2006.
 6. Dracup K, Alonzo AA, Atkins JM., et al: "The physician's role in minimizing prehospital delay in patients at high risk for acute myocardial infarction: Recommendations from the National Heart Attack Alert Program. Working Group on Educational Strategies To Prevent Prehospital Delay in Patients at High Risk for Acute Myocardial Infarction." *Annals of Internal Medicine*. 126(8):645–651, 1997.
 7. Lyle, KA: "The key to success in the chest pain emergency department: The observational role of nurse. Early Heart Attack Care Program (EHAC)." Available at St. Agnes Healthcare: <http://ehac.chestpain.org/st-agnes>.
 8. National Heart Attack Alert Program Coordinating Committee Access to Care Subcommittee: "Staffing and equipping emergency medical services systems: Rapid identification and treatment of acute myocardial infarction." *American Journal of Emergency Medicine*. 13(1):58–66, 1995.
 9. Alagona P, Altus P, Carrubba C, et al: "Prehospital actions by health-care providers and physicians." *Journal of the Florida Medical Association*. 82(2):100–107, 1995.
 10. Gotsman MS, Rozenman Y, Admon D, et al: "Changing paradigms in thrombolysis in acute myocardial infarction." *International Journal of Cardiology*. 59(3):227–242, 1997.
 11. Grijseels EWM, Deckers JW, Hoes AW, et al: "Prehospital triage of patients with suspected myocardial infarction: Evaluation of previously developed algorithms and new proposals." *European Heart Journal*. 16: 325–332, 1995.
 12. Aufderheide T, Kereiaker D, Weaver WD, et al: "Planning, implementation and process monitoring for prehospital 12-lead ECG diagnostic programs." *Prehospital and Disaster Medicine*. 11:162–171, 1996.
 13. Wuerz R, Meador SA: "Evaluation of a prehospital chest pain protocol." *Annals of Emergency Medicine*. 26:595–597, 1995.
 14. Emergency Department: "Rapid identification and treatment of patients with acute myocardial infarction." *Annals of Emergency Medicine*. 23(2):311–329, 1994.
 15. Selker HP, Zalenski RJ, Antman EM, et al: "An evaluation of technologies for identifying acute cardiac ischemia in the emergency department: A report from a National Heart Attack Alert Program Working Group." *Annals of Emergency Medicine*. 29(1):1–12, 1997.
 16. Canto JG, Rogers WJ, Bowlby LJ, et al: "The prehospital electrocardiogram in acute myocardial infarction: is its full potential being realized?" *National Registry of Myocardial Infarction 2 Investigators. Journal of American College of Cardiology*. 29(3):498–505, 1997.
 17. Aufdehiede TP, Keelan MH, Hendley GE, et al: "Milwaukee Prehospital Chest Pain Project—Phase I: Feasibility and accuracy of prehospital thrombolytic candidate selection." *American Journal of Cardiology*. 69(12):991–996, 1992.
 18. Foster DB, Dufendach JH, Barkdoll CM, et al: "Prehospital recognition of AMI using nurse/paramedic 12-lead ECG evaluation: Impact on in-hospital times to thrombolysis in a rural community hospital." *American Journal of Emergency Medicine*. 12(1):25–31, 1994.
 19. Wall TC, Albright J, Jacobowitz S, et al: "Prehospital ECG transmission speeds reperfusion for patients with acute myocardial infarction." *North Carolina Medical Journal*. 61:104–108, 2000.
 20. Weaver WD, Cerquiera M, Hallstrom AP, et al for the MITI Project Group: "Early treatment with thrombolytic therapy: Results from the myocardial infarction, triage and intervention prehospital trial." *JAMA*. 270:1211–1216, 1993.
 21. The European Myocardial Infarction Project Group: "Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction." *The New England Journal of Medicine*. 329(6):383–389, 1993.
 22. Trent R, Adams J, Rawles J: "Electrocardiographic evidence of reperfusion occurring before hospital admission. A Grampian Region Early Anistreplase Trial (GREAT) substudy." *European Heart Journal*. 15(7):895–897, 1994.
 23. Coccolini S, Berti G, Bosi S, et al: "Prehospital thrombolysis in rural emergency room and subsequent transport to coronary care unit: Ravenna myocardial infarction (RaMI) trial." *International Journal of Cardiology*. 49(Suppl.):S47–58, 1995.
 24. McAleer B, Ruane B, Burke E, et al: "Prehospital thrombolysis in a rural community: Short- and long-term survival." *Cardiovascular Drugs and Therapy*. 6(4):369–372, 1992.

25. Rozenman Y, Gotsman MS, Weiss AT, et al: "Early intravenous thrombolysis in acute myocardial infarction: The Jerusalem experience." *International Journal of Cardiology*. 49(Suppl.):S21–28, 1995.
26. Grim P, Feldman T, Martin M, et al: "Cellular telephone transmission of 12-lead electrocardiograms from ambulance to hospital." *American Journal of Cardiology*. 60(8):715–720, 1987.
27. Vaught C, Young DW, Bell SJ, et al: "The failure of years of experience with ECG transmission from paramedics to the hospital emergency department to reduce the delay from door to primary coronary intervention during acute myocardial infarction below the 90 minute threshold." *Journal of Electrocardiology*. 39(2):136–141, 2006.
28. Sejersten M, Young D, Clemmensen P, et al: "Comparison of the ability of paramedics with that of cardiologists in diagnosing ST-segment elevation acute myocardial infarction in patients with acute chest pain." *American Journal of Cardiology*. 90:995–998, 2002.
29. Pettis K, Kwong M, Wagner G: "Prehospital diagnosis and management of patients with acute myocardial infarction using remote transmission of electrocardiograms to palmtop computers." (Clement book). *ECG in Acute Myocardial Infarction*. p. 223–234, 1998.
30. Clemmensen P, Sejersten M, Sillesen M, Hampton D, Wagner GS, Loumann-Nielsen S: "Diversion of ST-elevation myocardial infarction patients for primary angioplasty based on wireless prehospital 12-lead electrocardiographic transmission directly to the cardiologist's handheld computer: a progress report." *Journal of Electrocardiology*. 38(Suppl.):194–108, 2005.
31. Campbell PT, Patterson J, Cromer D, et al: "Prehospital triage of acute myocardial infarction: Wireless transmission of electrocardiograms to the on-call cardiologist via a handheld computer." *Journal of Electrocardiology*. 38:300–309, 2005.
32. Aldrich HR, Wagner NB, Boswick J, et al: "Use of initial STsegment deviation for the prediction of final electrocardiographic size of acute myocardial infarcts." *American Journal of Cardiology*. 61:749–753, 1988.
33. Selvester RH, Wagner GS, Hindman NB: "The development and application of the Selvester QRS scoring system for estimating myocardial infarct size." *Archives of Internal Medicine*. 145:1877–1881, 1985.
34. Clemmensen PM, Ohman EM, Sevilla DC, et al: "Importance of early and complete reperfusion to achieve myocardial salvage after thrombolysis in acute myocardial infarction." *American Journal of Cardiology*. 70:1391–1396, 1992.
35. Sevilla DC, Wagner NB, Pieper KS, et al: "Use of the 12-lead electrocardiogram to detect myocardial reperfusion and salvage during acute myocardial infarction." *Journal of Electrocardiology*. 25:281–286, 1992.
36. The GUSTO Investigators: "An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction." *The New England Journal of Medicine*. 329:673–682, 1993.
37. Adams GL, Campbell P, Adams J, et al: "Prehospital Wireless Transmission of Electrocardiograms to a Cardiologist via Handheld Device for Patients with Acute Myocardial Infarction; the Timely Intervention in Myocardial Emergency, North East Experience (TIMENE)." *Journal of the American College of Cardiology*. 47(4):383A, 2006.
38. Strauss DG, Sprague PQ, Underhill K, et al: "Direct call from ambulance to coronary care unit to initiate primary percutaneous intervention for ST-elevation myocardial infarction." *Academic Emergency Medicine*. 13(5):S14, 2006.
39. Califf RM, Lee KL: "Data and safety monitoring committees: Philosophy and practice." *American Heart Journal*. 141:154, 2001.
40. Wilkins ML, Pryor AD, Maynard C, et al: "An electrocardiographic acuteness score for quantifying the timing of a myocardial infarction to guide decisions regarding reperfusion therapy." *American Journal of Cardiology*. 75:617–620, 1995.
41. Birnbaum Y, Maynard C, Wolfe S, et al: "Terminal QRS distortion on admission is better than ST segment measurements in predicting final infarct size and assessing the potential effect of thrombolytic therapy in anterior wall acute myocardial infarction." *American Journal of Cardiology*. 84:530–534, 1999.
42. Corey KE, Maynard C, Pahlm O, et al: "Combined historical and electrocardiographic timing of anterior and inferior wall acute myocardial infarcts for prediction of reperfusion achievable size limitation." *American Journal of Cardiology*. 83:826–831, 1999.
43. Pettis KR, Savona MR, Leibrandt PN, et al: "Evaluation of the efficacy of hand-held computer screens for cardiologists' interpretations of 12-lead electrocardiograms." *American Heart Journal*. 138:765–770, 1999.
44. Leibrandt PN, Bell SJ, Savona MR, et al: "Validation of cardiologist's decisions to initiate reperfusion therapy for acute myocardial infarction using ECGs on liquid crystal displays hand held computer as decision support regarding reperfusion therapy for acute myocardial infarction." *American Heart Journal*. 140:747–752, 2000.

Chapter 4

Prehospital triage of acute myocardial infarction: wireless transmission of electrocardiograms to the on-call cardiologist via a handheld computer

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ABSTRACT

Background: Use of intravenous fibrinolytic agents and percutaneous coronary interventions produce the greatest benefit when they are implemented in the first 2 hours after symptom onset. Further delays in the time to treatment typically lead to reduced benefits and poorer outcomes.

Methods: Cabarrus County Emergency Medical Service personnel complete an acute myocardial infarction case report form and assess a 12-lead electrocardiogram (ECG) to determine if ST elevation of at least 1 mV in at least 2 contiguous leads is present and then to transmit the ECG wirelessly to the emergency department (ED). The ECG is then forwarded wirelessly from the ED to the on-call cardiologist who is carrying the IPAQ hand-held computer.

Results: Five representative patients managed using this system during the initial year of its implementation are presented.

Conclusion: The examples included in this article illustrate that the system and technology can work if applied in a coordinated fashion using multiple disciplines including emergency medical service, cardiologists, ED personnel, and the hospital cardiac care team, which includes the catheterization laboratory call team, acute coronary care nurses, and clerical support staff.

INTRODUCTION

Over the last 2 decades, treatment advances using pharmacologic and mechanical reperfusion strategies have improved the treatment of acute myocardial infarction (AMI) significantly. Use of intravenous fibrinolytic agents and percutaneous coronary interventions (PCIs) produce the greatest benefit when they are implemented in the first 2 hours after symptom onset (1-6). Further delays in the time to treatment typically lead to reduced benefits and poorer outcomes. Reducing the time to treatment is thus a major component in the triage and treatment of the patient with an AMI.

A new digital electrocardiogram (ECG) imaging and information system was devised that links a county's emergency medicine system paramedics to on-call cardiologists. This system allows early notification and assembly of the cardiac team before patient arrival to the hospital to facilitate direct transport to the catheterization laboratory (cath lab). This new system has reduced the door-to-dilation time in several patients. This initial report describes the system and shows examples of its effectiveness in a subset of patients encountered.

BACKGROUND

Numerous strategies have been used in the past to reduce the time from the acute coronary thrombotic occlusion onset to definitive therapy. These include community educational initiatives (7-9), specific AMI protocol development for emergency departments (EDs) (10-16), prehospital ECG transmission from emergency medical service (EMS) vehicles to EDs (17-20), and prehospital fibrinolytic therapy (21-26).

Electronic transmission of ECGs to receiving stations in hospitals have been implemented since 1987 (27). The Timely Intervention in Myocardial Emergency (TIME) Trial (20) documented a 27% (109 to 80 minutes) reduction of time from EMS paramedic arrival scene to successful PTCA by implementing prehospital ECG transmission to the ED. Electrocardiogram transmission directly to the cardiology specialist responsible for the patient's in-hospital care via a wireless modem, however, has only recently become an option (28). This system provides parallel ECG transmission to the ED and the cardiologist on-call. Studies were required to determine if the cardiologist would be capable of making the same diagnostic and therapeutic decisions when viewing ECGs on the liquid crystal display of a handheld device as on conventional ECG paper.

Similar ECG interpretation and decision regarding initiation of reperfusion therapy have been reported (29,30). The technology implemented in this report includes ECG wireless transmission from a Welch Allyn Portable Intensive Care System (Welch Allyn PIC 50, Buffalo Grove, IL, USA) cardiograph to the cardiologist on-call equipped with a handheld computer (Pocket PC).

METHODS

The devices

A Hewlett-Packard IPAQ 3850 Pocket PC in conjunction with a Verizon (Verizon Wireless, Alpharetta, GA, USA) 555 AirCard is used by on-call cardiologists to receive 12-lead ECGs transmitted from the field. Adobe Acrobat Reader is installed to view the ECG. The Welch Allyn SmartLink Wireless 12-lead Server enables the user to view all 12 leads of the ECG simultaneously or enlarge a specific lead for individual analysis.

County EMS ambulances are each equipped with a Welch Allyn Portable Intensive Care System (Welch Allyn PIC 50). Electrocardiograms are obtained at the scene and the ECG data are transmitted to a Pocket PC device via a serial cable from the mobile monitor. The Pocket PC runs an application called eSynch designed by Welch Allyn. The application collects the data from the mobile monitor. The EMS paramedic then opens the Verizon connection software on the Pocket PC and initiates the connection to the Verizon 1XRTT voice/data network. The data are sent across the Internet and received by the Welch Allyn SmartLink Wireless Server in the ED.

Emergency medical service paramedics notify the ED charge nurse of the incoming ECG. The Welch Allyn SmartLink Wireless 12-lead Server displays the ECG, creates an audible alarm and prints the ECG to a network printer. The ED nurse then saves the ECG as a PDF file and sends the file to the on-call cardiologist using e-mail. The ED nurse then pages the on-call cardiologist to notify of an incoming ECG. Each cardiologist has a unique POP3 e-mail account, which can be checked from a wireless Pocket PC. If the on-call cardiologist is in the hospital when an ECG is sent, he or she can use the hospital's 802.11b WiFi network to connect to the Internet to receive the ECG. The Pocket PCs are equipped with WiFi to allow this option.

The steps required by the receiving cardiologist are:

1. Receive a page alerting that an ECG transmission is on-route.
2. The Pocket PC is turned on, connected to either intra- or internet, and checked for bin-comingQ mail.
3. The ECG is accessed using Adobe Acrobat Reader for Pocket PC in the 3 simultaneous lead format.
4. Scroll through the 4 sequential 3 lead fields to view the entire 12-lead recording.
5. Focus on the set of leads that reveal the maximal STsegment deviation indicating the acute injury current.
6. Determine if the threshold for administering reperfusion therapy is met (at least 1 mV ST elevation in at least 2 contiguous leads).
7. If this ECG review is diagnostic of AMI, the cardiologist communicates with the EMS paramedic to determine if the patient is a candidate for catheterization.

- If this decision is affirmative, communication to the EMS paramedic, ED, and cardiac team is simultaneously activated.

Data collection

All patients with an ST-elevation AMI diagnosis by EMS paramedics have their ECG recording wirelessly transmitted to the ED and the cardiologist on-call. A flow diagram demonstrating the sequence of information transfer and processing is shown in Figure 1. Emergency medical service paramedics use a call report form (Figure 2) to gather information on each patient presenting to the EMS with chest pain. This form notes the times of symptom onset, prehospital ECG, and arrival to the hospital as well as symptoms, patient history, and other pertinent clinical data. A research nurse from the NorthEast Medical Center (NEMC) is responsible for completing a cath lab report form (Figure 3) for each patient who undergoes interventional treatment. The form includes procedural times, treatment outcomes, complications, and other medical findings documented during primary PCI.

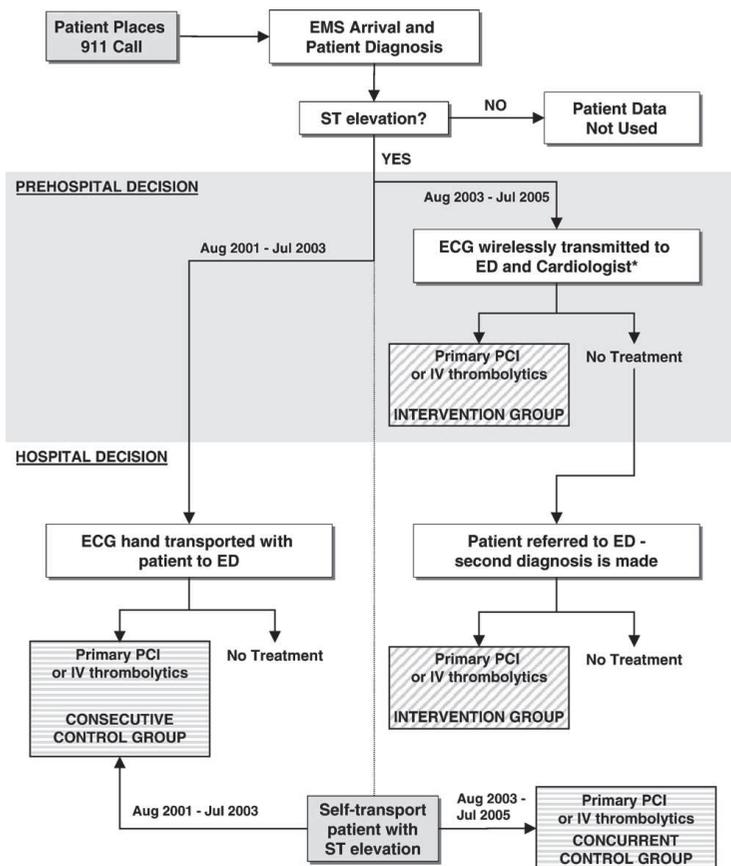


Figure 1: Patient Selection for TIME NE Study.

The participants

NorthEast Medical Center is a 457-bed medical center with 2 cath labs that are equipped for adult interventional cardiac catheterization. In these laboratories, 4 interventional cardiologists perform approximately 250 primary PTCA procedures annually. All patients transported by the Cabarrus County EMS with acute chest pain have ECGs done, and those with ST elevation of at least 1 mV in at least 2 contiguous leads have their ECGs transmitted and care dictated by Cabarrus County EMS cardiac care protocols.

Cabarrus County EMS paramedics complete an AMI case report form for all patients they consider to be possibly experiencing an AMI (Figure 1). They determine if ST elevation of at least 1mV in at least 2 contiguous leads is present on a standard 12-lead ECG. They transmit the ECG to the Welch Allyn SmartLink Wireless Server located in the ED and immediately inform the ED personnel that transmission is in progress. The ECG is then forwarded by an ED nurse from the Welch Allyn SmartLink Wireless Server to the receiving IPAQ device. Emergency medical service paramedics then communicate with the cardiologist via the ED contact for patient care instructions. The patient is transported directly to the cath lab if instructed by the cardiologist on-call to bypass the ED.

Cabarrus County EMS							
Acute MI							
TIME Trial II							
Unit _____ Date ____/____/____							
Patient's Name _____ Age: _____							
Patient's Cardiologist: _____ MR# _____ Acct# _____							
Assessment:							
Note: Location/description, risk/precipitating factors, associated symptoms determined should be recorded on ACR.							
1)	Y	N	Typical/classical chest discomfort?	10)	Y	N	Family history of Heart Disease
2)	Y	N	Is Chest Pain the Primary Complaint?	11)	Y	N	Elevated Cholesterol
3)	Y	N	Radiation of Pain	12)	Y	N	Oriented, can cooperate?
4)	Y	N	Has discomfort been constant?	13)	Y	N	h/o CABG
5)	Y	N	Nausea/vomiting				When? _____
6)	Y	N	Diaphoresis or SOB (circle one)				Where? _____
7)	Y	N	hypertension	16)	Y	N	h/o PTCA/Stent
8)	Y	N	Past or Current smoker				When? _____
9)	Y	N	h/o diabetes				Where? _____

Call Received: _____; _____

Approx. Time of Sx. onset: _____; _____

Time of EMS 12 Lead: _____; _____

Time Of Arrival in ED _____; _____

Pick-up Point of Origin _____

Medications (name, dose and interval): _____

****BRING ALL MEDICATION TO CATH LAB****

Vital Signs/ECG Tracing:

BP: _____ / _____ Pulse: _____ Respirations: _____

(circle one)

19) Does the 12 lead ECG indicate acute myocardial infarction? Yes _____ No _____

20) ECG transmitted to ED? Yes/Time _____ No _____

21) ECG transmitted to on call cardiologist? Yes/Time _____ No _____

22) Successful phone contact made with cardiologist? Yes/Time _____ No _____

History:

Y N Pregnant?

Y N Hx of Bleeding Problems?

Y N CVA, Brain Surgery, Brain Tumor or Seizure Hx?

Y N Hospitalized in last 2 months? If yes, Why? _____

Y N Hx of Recent GI Bleed (<10 days)?

Y N Recent Surgery/Trauma (in last 3-mo.)?

Y N Previous Rx with Thrombolytics?

Y N Takes blood thinners? (Coumadin, Warfarin)

Y N History of renal failure?

Y N Contrast Allergies?

Y N Femoral/D. Pedis pulses present?

Office Use Only
Intervention Control

Figure 2: Cabarrus County EMS Call Report Form.

The catheterization call team responds to the activation call and receives the patient from EMS paramedics in the cath lab. The study nurse collects the requested study related data on all patients receiving primary PCI or IV fibrinolytics and transported to NEMC by Cabarrus County EMS.

CASES

Case 1

A 59-year-old man with history of sleep apnea and hyperlipidemia developed substernal chest pain while lifting weights at 6:30 pm at his local gym. He went home and his daughter called 911. Emergency medical service paramedics arrived at 6:57 pm. A 12-lead ECG was obtained in the patient's bedroom, which showed acute anterior injury pattern. This ECG was transmitted to the ED at 7:19 pm and immediately forwarded to the on-call cardiologist. The ECG was reviewed on the cardiologist's IPAQ, pertinent clinical data were reviewed, and the patient was determined to be a primary PCI candidate. The order was given to proceed directly to the cath lab. The patient arrived at the cath lab at 7:35 pm. Coronary cineangiograms revealed an occluded proximal left anterior descending, minor irregularities in the left circumflex, and 25% stenoses in the right coronary artery. The left anterior descending was angioplastied open with TIMI (Thrombolysis in Myocardial Infarction) 3 flow at 8:08 pm (33 minutes door-to-dilation time), with subsequent stenting (Figure 4). Left ventriculogram showed mild anterior and moderate lateral hypokinesia (left ventricular ejection fraction [LVEF] = 45%).

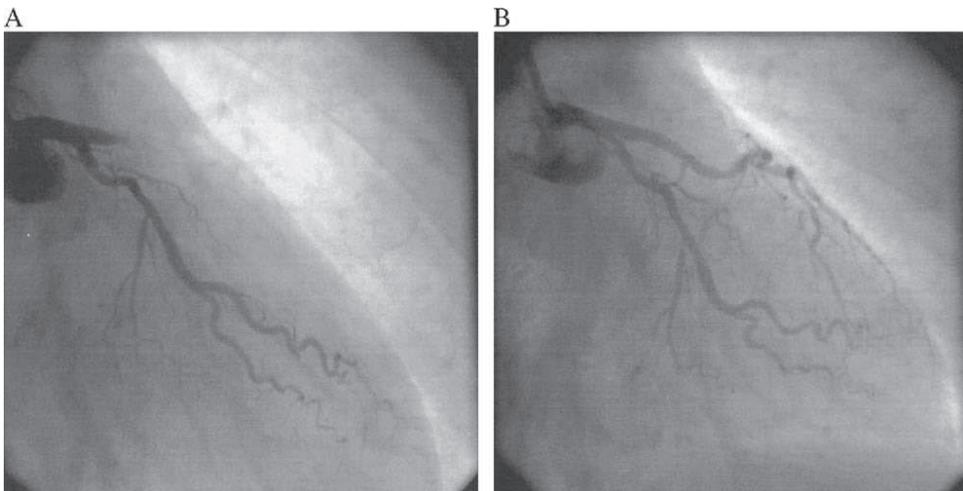


Figure 4: Left coronary angiogram in the right anterior oblique view for Case #1. In A prior to the percutaneous coronary intervention showing complete occlusion of the anterior descending branch and in B following stent deployment.

Case 2

A 53-year-old man with a history of hypertension and smoking developed chest pain. The pain resolved within 10 to 15 minutes only to recur the next day. He presented to his primary care physician's office within 1 hour of onset of symptoms. A 12-lead ECG obtained by EMS paramedics at 11:40 am revealed an anterior injury pattern (Figure 5). The ECG was transmitted to the ED and immediately forwarded to the cardiologist. The patient arrived at the cath lab at 12:02 pm. Coronary cineangiograms revealed a 99% mid left anterior descending lesion with TIMI 3 flow with contrast injection at 12:29 pm (27 minutes, door-to-reperfusion time), 25% and 50% left circumflex stenoses, and 50% and 25% right coronary stenoses. The left anterior descending was subsequently stented to 0% residual. Left ventriculogram revealed an LVEF of 35% to 40% with severe lateral hypokinesia and moderate anterior and apical hypokinesia.

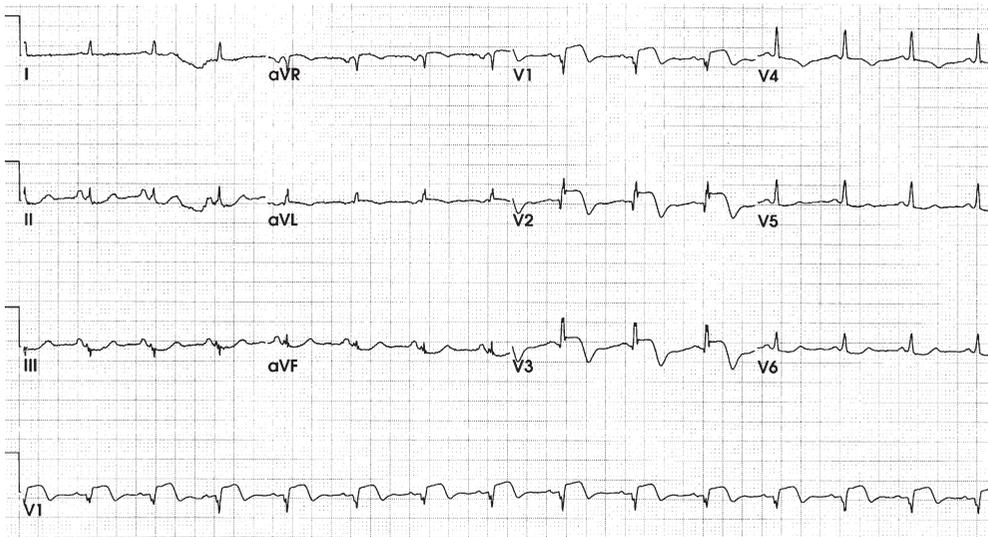


Figure 5: The presenting prehospital ECG for Case #2. Note ST segment elevation in leads V1–V4.

Case 3

A 44-year-old man with a history of smoking developed substernal chest pain at 7:00 am. Emergency medical service paramedics were summoned at 8:11 am, arrived at the scene at 8:15 am, and a 12-lead ECG revealed an acute inferior injury pattern at 8:20 am. The patient was sent directly to the cath lab with arrival at 8:58 am. Coronary cineangiograms revealed a 99% mid right coronary artery stenosis with TIMI 3 flow at 9:31 am (33 minutes, door-to-reperfusion time), a normal left circumflex, and a 50% mid left anterior descending lesion. The right coronary artery was stented to 0%. Left ventriculogram revealed mild inferobasal hypokinesia with an LVEF of 55% to 60% (Figure 6).

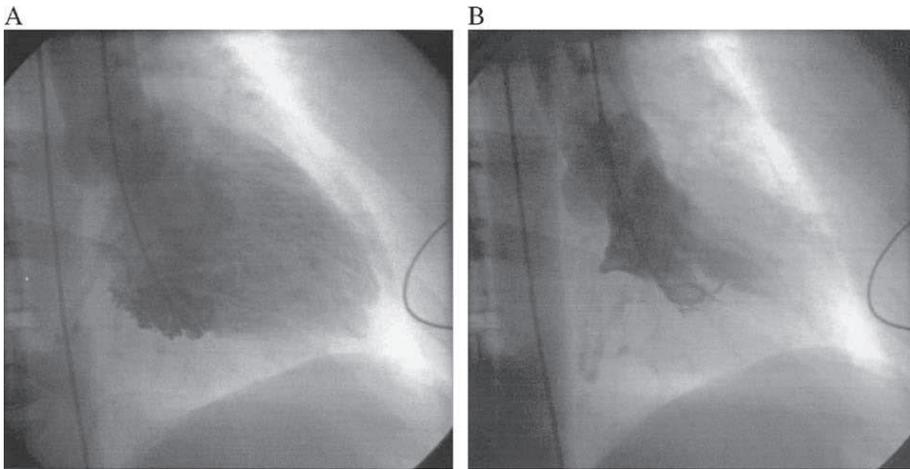


Figure 6: Left ventriculogram in the right anterior oblique views for Case #3 in diastole (A) and systole (B). Since there was only mild inferobasal hypokinesis there is normal left ventricular ejection.

Case 4

A 48-year-old man with a history of hypercholesterolemia, hypertension, and smoking had an abrupt onset of chest pain at 7:00 am (Figure 7). Emergency medical service paramedics were called and a 12-lead ECG was obtained in the field revealed acute inferior injury pattern at 7:36 am (Figure 7). The patient was directed straight to the cath lab with arrival at 8:07 am. Coronary cineangiograms revealed an occluded mid right coronary artery, a 50% mid left circumflex stenosis, and a 25% mid left anterior descending stenosis. The right coronary artery was opened with guidewire passage at 8:25 am (27 minutes, door-to-reperfusion time) with subsequent angioplasty and stenting. Left ventriculogram showed mild inferior and posterior hypokinesis with an LVEF of 55%.

Case 5

A 67-year-old man with a history of hypertension, cigar smoking, and peripheral vascular disease developed substernal chest pain while shoveling snow at 3:30 pm. A 12-lead ECG was obtained and sent digitally to the cardiologist on call at 3:58 pm (Figure 8). The patient was referred directly to the cath lab with arrival at 4:03 pm. Coronary cineangiograms at 4:33 pm (30 minutes) showed a 99% mid left anterior descending stenosis with TIMI 2 flow, a 50% left circumflex stenosis, and a 75% mid right coronary artery lesion. The patient underwent angioplasty of his left anterior descending lesion reducing the 99% stenosis to a minor irregularity with subsequent normal TIMI 3 flow at 4:38 pm (35 minutes, door-to-reperfusion time). Left ventriculogram revealed moderate anterior and lateral hypokinesis with an LVEF of 40% to 45%.

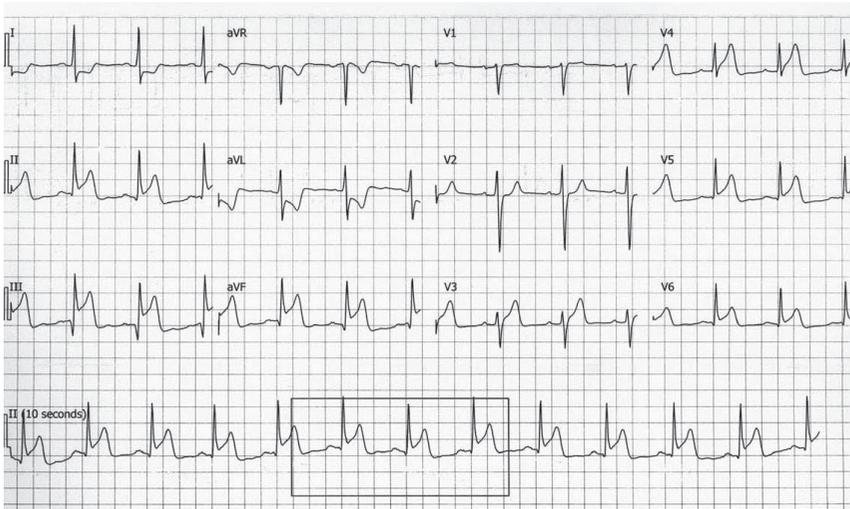


Figure 7: The presenting prehospital ECG for Case #4. Note ST elevation in II, III, aVF, and V3–V6.

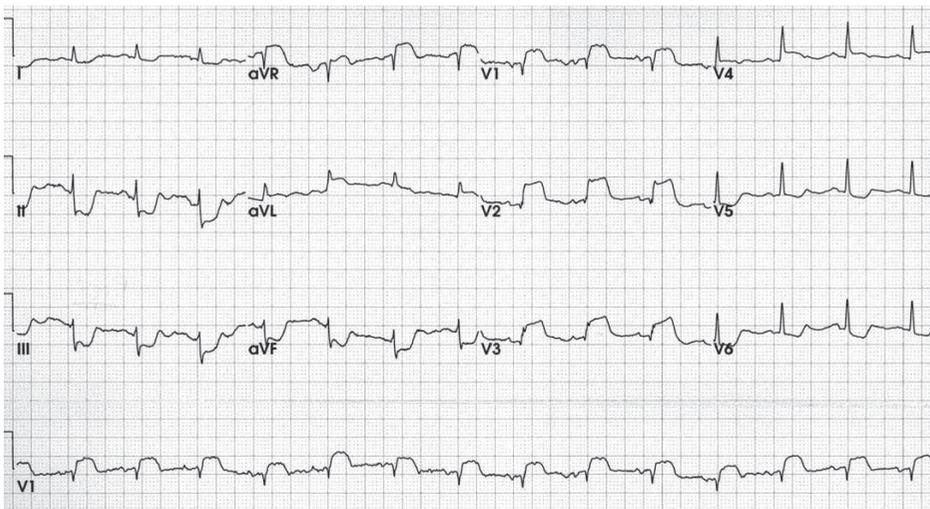


Figure 8: The presenting prehospital ECG for Case #5. Note ST elevation in aVR and V1 to V3.

DISCUSSION

Much progress has been made over the past 2 decades in the treatment of AMI. The 1980s saw a significant advancement with the widespread use of fibrinolytic pharmacologic strategies to treat coronary thromboses. Despite these advances, success rates are at best 50% to 60% with a pharmacologic approach (31,32). The 1990s saw the advancement of PCI with the introduction of primary angioplasty and subsequent primary stenting (33–35). Major limiting steps in the treatment of AMI with primary PCI are patient recognition

of and response to the signs and symptoms of AMI, activation of EMS, efficient transfer to the cath lab, and preparation for primary PCI with subsequent expeditious coronary imaging and intervention. According to the National Registry of Myocardial Infarction, the national average door-to-dilation time has been in the 100- to 105-minute range with a goal of less than 90 minutes (36). These median times give an indication as to the limited number of patients actually reperfusing within the first 2 hours of symptom onset. A system which minimizes delays in treatment and incorporates the input of a cardiologist and cardiac care team as early as possible will likely result in a significant improvement in time to reperfusion.

This report introduces a new systematic approach to the patient experiencing an AMI using state-of-the-art technology with wireless ECG transmission as well as the assembly of a cardiac care team, before the patient arrives at the hospital. This allows a number of patients to bypass the ED and thereby leads to a reduction in time delays in the treatment of this patient population. The examples included in this article illustrate that the system and technology can work if applied in a coordinated fashion using multiple disciplines including county EMS, cardiologists, ED personnel, and the cardiac care team.

Patient identification of the signs and symptoms of AMI and activation of the EMS via 911 is critical for this system to be applied. At present, approximately one third of AMI patients in Cabarrus County use 911 to allow transport via EMS ambulance. Educational efforts are ongoing to rectify this.

These cases are included in an ongoing study comparing a previous treatment approach (control data) to the new system described above. Door-to-reperfusion times and outcomes including myocardial salvage will be assessed. It is hoped that as technologies continue to evolve allowing the activation of cardiac teams even more quickly before hospital arrival, improved myocardial salvage, function, and survival will result for AMI patients (37).

REFERENCES

1. Brodie BR, Stuckey TD, Wall TC, et al. Importance of time to reperfusion for hospital and long term survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction [Abstract]. *Circulation* 1997;96(8):I-32.
2. Suryapranata H, Liem L, van't Hof AWJ, et al. The influence of time to treatment in patients with acute myocardial infarction treated with primary angioplasty [Abstract]. *Circulation* 1997;96(8):I-32.
3. Boersma E, Maas ACP, Deckers JW, et al. Early thrombolytic treatment in acute myocardial infarction: appraisal of the golden hour. *Lancet* 1996;348:772.
4. Selig MB. Early management of acute myocardial infarction: thrombolysis, angioplasty, and adjunctive therapies. *Am J Emerg Med* 1996;14(2):209.
5. Julian DG. Time as a factor in thrombolytic therapy. *Int J Cardiol* 1995;49(Suppl):S17.
6. Rawls JM. Quantification of the benefit of earlier thrombolytic therapy: five year results of the Grampian Region Early Anistreplase Trial (GREAT). *J Am Coll Cardiol* 1997;30(5):1181.
7. Dracup K, Alonzo AA, Atkins JM, et al. The physician's role in minimizing prehospital delay in patients at high risk for acute myocardial infarction: recommendations from the National Heart Attack Alert Program.

- Working Group on Educational Strategies To Prevent Prehospital Delay in Patients at High Risk for Acute Myocardial Infarction. *Ann Intern Med* 1997;126(8):645.
8. Lyle KA. The key to success in the chest pain emergency department: the observational role of nurse. Early Heart Attack Care Program (EHAC)—Internet site (<http://ehac.chestpain.org/st-agnes>)—St Agnes Healthcare.
 9. Staffing and equipping emergency medical services systems: rapid identification and treatment of acute myocardial infarction. National Heart Attack Alert Program Coordinating Committee Access to Care Subcommittee. *Am J Emerg Med* 1995;13(1):58.
 10. Alagona P, Altus P, Carrubba C, et al. Prehospital actions by healthcare providers and physicians. *JFMA* 1995;82(2):100.
 11. Gotsman MS, Rozenman Y, Admon D, et al. Changing paradigms in thrombolysis in acute myocardial infarction. *Int J Cardiol* 1997; 59(3):227.
 12. Grijseels EWM, Deckers JW, Hoes AW, et al. Pre-hospital triage of patients with suspected myocardial infarction: evaluation of previously developed algorithms and new proposals. *Eur Heart J* 1995; 16:325.
 13. Aufderheide T, Kereiaker D, Weaver WD, et al. Planning, implementation, and process monitoring for prehospital 12-lead ECG diagnostic programs. *Prehosp Disaster Med* 1996;11:162.
 14. Wuerz R, Meador SA. Evaluation of a prehospital chest pain protocol. *Ann Emerg Med* 1995;26:595.
 15. Emergency department: rapid identification and treatment of patients with acute myocardial infarction. *Ann Emerg Med* 1994;23(2):311.
 16. Selker HP, Zalenski RJ, Antman EM, et al. An evaluation of technologies for identifying acute cardiac ischemia in the emergency department: a report from a National Heart Attack Alert Program Working Group. *Ann Emerg Med* 1997;29(1):1.
 17. Canto JG, Rogers WJ, Bowlby LJ, et al. The prehospital electrocardiogram in acute myocardial infarction: is its full potential being realized? National Registry of Myocardial Infarction 2 Investigators. *J Am Coll Cardiol* 1997;29(3):498.
 18. Aufdehiede TP, Keelan MH, Hendley GE, et al. Milwaukee Prehospital Chest Pain Project—Phase I: feasibility and accuracy of prehospital thrombolytic candidate selection. *Am J Cardiol* 1992;69(12):991.
 19. Foster DB, Dufendach JH, Barkdoll CM, et al. Prehospital recognition of AMI using nurse/paramedic 12-lead ECG evaluation: impact on in-hospital times to thrombolysis in a rural community hospital. *Am J Emerg Med* 1994;12(1):25.
 20. Wall TC, Albright J, Jacobowitz S, et al. The TIME (Timely Intervention in Myocardial Emergency) Trial: reducing time to primary PTCA with the use of prehospital ECGs for patients with acute MI. *N C Med J* 2000;61:104.
 21. Weaver WD, Cerquiera M, Hallstrom AP, et al. Early treatment with thrombolytic therapy: results from the myocardial infarction, triage, and intervention prehospital trial. *JAMA* 1993;270:1211.
 22. The European Myocardial Infarction Project Group. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. *N Engl J Med* 1993;329:383.
 23. Trent R, Adams J, Rawles J. Electrocardiographic evidence of reperfusion occurring before hospital admission. A Grampian Region Early Anistreplase Trial (GREAT) sub-study. *Eur Heart J* 1994; 15(7):895.
 24. Coccolini S, Berti G, Bosi S, et al. **Prehospital thrombolysis in rural emergency room and subsequent transport to coronary care unit: Ravenna myocardial infarction (RaMI) trial.** *Int J Cardiol* 1995; 49(Suppl):S47.
 25. McAleer B, Ruane B, Burke E, et al. Prehospital thrombolysis in a rural community: short- and long-term survival. *Cardiovasc Drugs Ther* 1992;6(4):369.
 26. Rozenman Y, Gotsman MS, Weiss AT, et al. Early intravenous thrombolysis in acute myocardial infarction: the Jerusalem experience. *Int J Cardiol* 1995;49(Suppl):S21.
 27. Grim P, Feldman T, Martin M, et al. Cellular telephone transmission of 12-lead electrocardiograms from ambulance to hospital. *Am J Cardiol* 1987;60(8):715.
 28. Pettis K, Kwong M, Wagner G. Prehospital diagnosis and management of patients with acute myocardial infarction using remote transmission of electrocardiograms to palmtop computers (Clement book). *ECG Acute Myocardial Infarction* 1998;223.
 29. Pettis KR, Savona MR, Leibbrandt PN, et al. Evaluation of the efficacy of hand-held computer screens for cardiologists' interpretations of 12 lead electrocardiograms. *Am Heart J* 1999;138:765.
 30. Leibbrandt PN, Bell SJ, Savona MR, et al. Validation of cardiologist's decisions to initiate reperfusion therapy for acute myocardial infarction using ECGs on liquid crystal displays hand held computer as decision support regarding reperfusion therapy for acute myocardial infarction. *Am Heart J* 2000;140:747.
 31. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). **Effectiveness of Intrave-**

- nous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;1:397.
32. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *J Am Coll Cardiol* 1988;12:3A.
 33. Hartzler GO, Rutherford BD, McConahay DR, et al. Percutaneous transluminal coronary angioplasty with and without thrombolytic therapy for treatment of acute myocardial infarction. *Am Heart J* 1983;106:965.
 34. Meyer J, Merx W, Dorr R, et al. Successful treatment of acute myocardial infarction shock by combined percutaneous transluminal coronary recanalization (PTCR) and percutaneous transluminal coronary angioplasty (PTCA). *Am Heart J* 1982;103:132.
 35. Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med* 1993;328:673.
 36. Genentech, Incorporated. National Registry of Myocardial Infarction; NRMI-4 quarterly report September, 2003.1
 37. Participating cardiologists: Thomas F. Trahey, MD, Kevin R. Kruse, MD, David C. Beard, MD, Patrick K. Anonick, MD, Hans H. Lee, MD, Markus D. Scherer, MD, Thomas J. Christopher, MD, Christopher R. Kroll, MD.

Chapter 5

Comprehensive hospital care improvement
strategies reduce time to treatment in
ST-elevation acute myocardial infarction

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ABSTRACT

Background: Delay in treatment of patients with ST-elevation acute myocardial infarction (STEMI) has an adverse effect on patient outcomes. Limited data are available on the effectiveness of hospital care improvement strategies (HCIS) to reduce time to reperfusion by percutaneous coronary intervention (PCI). This study evaluated the combined effect of HCIS implementation to reduce door-to-balloon time in patients with STEMI.

Methods: Retrospective chart review was done for 95 consecutive patients with STEMI who underwent PCI at Charleston Area Medical Center. Patients with non-STEMI and patients transferred from other medical centers were excluded. Door-to-balloon time was defined as time from emergency department arrival to first PCI balloon inflation. A program of 3 HCIS was implemented: 1) a fast-track catheterization laboratory protocol, 2) feedback to cardiologists on their treatment times, and 3) a weekday 24-hour inhouse catheterization laboratory team. Patients were separated into groups before ($n = 46$), during ($n = 18$), and after ($n = 31$) HCIS implementation.

Results: Mean age was 60.3 ± 13 years and 74% were male. The majority (64%) arrived by ambulance; 29% had a prehospital electrocardiogram done. Most patients presented during the day (68%) on weekdays (75%). Symptom onset-to-door time was 289 ± 393 minutes. No significant differences were found between the groups for these variables. Door-to-PCI time in minutes was reduced in the group after versus the group before HCIS implementation (94.3 ± 37 vs 133.5 ± 53 ; $P < 0.0001$).

Conclusion: Implementation of HCIS shortened door-to-PCI time for patients with STEMI by 39.2 ± 10 minutes. Thus, HCIS may be effective in improving patient outcomes.

INTRODUCTION

Myocardial salvage is increased by reducing treatment delay for patients with ST-elevation acute myocardial infarction (STEMI) (1,2). Many causes for prehospital delay have been identified, including patient misinterpretation of symptoms and inability to obtain or transmit prehospital 12-lead electrocardiograms (ECGs) (3–5).

Inhospital delays between admission and administration of thrombolytic therapy have been associated with factors such as female gender, older age, and an increased prehospital delay have been identified (6), and measures have been found to be effective in reducing the time to thrombolytic therapy, including fast-track admission procedures as well as earlier ECG and enzyme testing for patients with suspected acute myocardial infarction (AMI) (7). However, the effectiveness of inhospital interventions has not been studied on reducing time to percutaneous coronary intervention (PCI).

The aim of the current study was to evaluate the effect of a combination of 3 hospital care improvement strategies (HCIS) on treatment time to reperfusion by PCI: 1) catheterization laboratory staffing during off hours (8), 2) individualized feedback on treatment times to cardiologists on a quarterly basis, and 3) a fast-track protocol for patients with AMI using a “cardiac alert” paging system (similar to a trauma call).

METHODS

This study was approved by the West Virginia University Institutional Review Board. From January 1, 2003, through May 18, 2004, AMI was identified in 96 patients from the Centers for Medicare & Medicaid Services (CMS) database (9) at Charleston Area Medical Center (CAMC). The inclusion criteria were STEMI at admission as determined by ECG or emergency department (ED) physician diagnosis followed by PCI. Patients transferred from other hospitals and patients undergoing thrombolytic therapy or bypass surgery were not included in this study. One patient with an outlying door-to-balloon time of >12 hours as a result of an incorrect initial diagnosis by the ED physician was excluded. Chart review was done for all patients to verify the clinical data and to validate the time parameters.

The call system at CAMC has been in place for more than 5 years and included 33 cardiologists in 6 call groups for their own patients and in 5 call groups for the unassigned patients. Thirteen of the cardiologists were interventionalists. When a noninterventionalist was on call, there would be an interventionalist assigned as backup.

Interventions

The 3 interventions were done over a 60-day period (Figures 1 and 2).

1. Fast-track protocol for patients with AMI (September 17, 2003). For all patients eligible for emergency reperfusion therapy, as determined by the ED physician, a “cardiac alert” code was to be called. The ED physician initiated the cardiac alert, sending a preset multiple pager message through the hospital operator to the on-call cardiologist, the catheterization laboratory coordinator, the ECG technician, the laboratory technician, the radiology technician, and the ED registration clerk. Before this intervention there was no protocol for activation of the catheterization laboratory, this was left to the discretion of the on-call cardiologist and the ED physician.
2. Individualized quarterly feedback on treatment times to cardiologists (November 11, 2003). The feedback included the times to treatment. Cardiologists had access to their own data and the average of all cardiologists practicing at CAMC.
3. Weekday 24-hour inhouse catheterization laboratory team (November 23, 2003). Before this, the catheterization laboratory was staffed from 7:00 AM to 7:00 PM on weekdays and catheterization laboratory personnel were on call offsite during offhours.

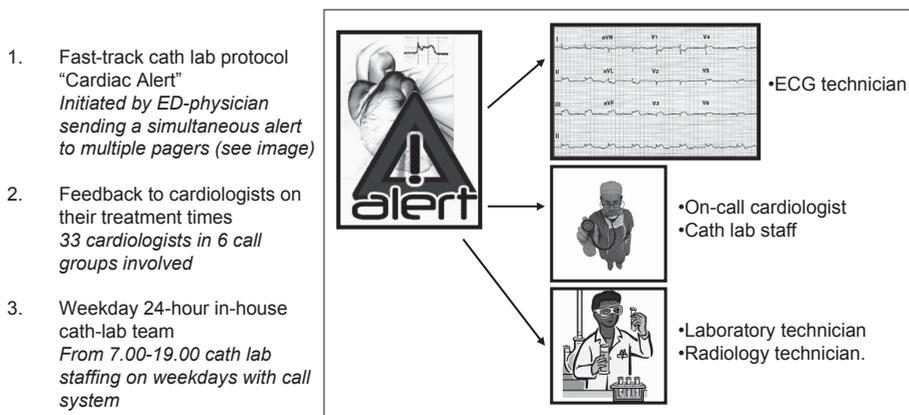


Figure 1: Hospital care improvement strategies. The “cardiac alert” simultaneous paging protocol is displayed on the right.

Increased catheterization laboratory scheduling for a radiation technician, a scrub nurse, a unit coordinator, and a registered nurse is estimated at \$120,000 U.S. per year. Introduction of the first 2 initiatives required time from the hospital care quality director, but no extra costs because they involved reorganizing the care that was already available.

Evaluation of Effectiveness

Previously reported factors with the potential to affect times to treatment (4–8) were collected, including age, gender, mode of transport, prehospital 12-lead ECG, and time of symptom onset.

Door-to-balloon time was used as the primary outcome measure and was defined as the time between ED arrival to the time of first PCI balloon inflation. Additional outcome measures included death (assessed by review of the social security death registry at 3 months after the last patient was included), symptom onset to balloon time, and door-to-ECG time.

Outcomes of patients before ($n = 46$) and after ($n = 31$) implementation of the 3 HCIS was evaluated, excluding patients admitted during the implementation period ($n = 18$). To evaluate the use and effectiveness of the cardiac alert, the paging log of the telephone operator was used to compare the door-to-balloon time of study patients with and without initiation of the cardiac alert system.

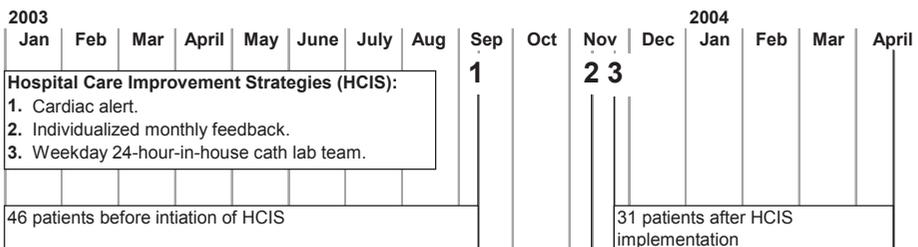


Figure 2: Implementation of hospital care improvement strategies. The number in the figure corresponds with the number of the care improvement strategy and indicates the order in which it was implemented.

The effect of the 24-hour inhouse catheterization laboratory during weekdays was evaluated by comparing outcomes for patients arriving during weekday nights before and after implementation of inhouse catheterization laboratory personnel.

Statistical Analysis

SPSS (version 12.0, SPSS Inc.) was used for all analysis. Student t test was used to compare continuous variables between the patient groups. Chi-square test was used for the categorical variables. Multivariate linear regression was done to account for differences in the baseline characteristics when present, and logistic regression was used to determine significant predictors of less treatment delay. $P < 0.05$ was considered statistically significant. Results are presented as mean \pm standard deviation (SD), frequencies, or percentages. Time differences are presented as mean \pm standard error (SE).

RESULTS

Data were analyzed for 95 consecutive patients from January 1, 2003, to May 18, 2004. Baseline characteristics are displayed in Table 1: Average age was 60.3 ± 13 years, 24.2% were 70 years or older, and 73.7% were male. Patients arrived by ambulance in 64.2% of the cases; a prehospital ECG was done in 29.5%. Retrospective ECG analysis revealed a total ST deviation of 16.0 ± 10 mV, the mean heart rate was 75 ± 20 , and QRS duration was 95 ± 17 ms.

Most patients arrived between 7 AM and 7 PM (68.4%) and from Monday through Friday (74.7%). The mean time from symptom onset to ED presentation was 289.5 ± 393 minutes.

Mean door-to-balloon time for all patients was 123.1 ± 61 minutes and mean time from door to first ECG was 10.7 ± 12 minutes. Three patients (3.2%) died in the follow-up period (July 2004).

Forty-six patients admitted from January 1, 2003, through September 16, 2003, were compared with 31 patients admitted from November 23, 2003, through April 18, 2004. The 3 HCIS were implemented during the transition period (September 17 through November 22). The results are displayed in Table 2. Mean door-to-PCI time in minutes and mean door-to-ECG time were reduced in the patients after HCIS implementation compared with

Table 1: Baseline characteristics

	All patients (n=95)	Before HCIS (n=46)	After HCIS (n=31)	P-value
Age (years)	60.3 ± 13	61.4 ± 12	57.1 ± 12	0.13
Age >70 (%)	24.2	28.3	12.9	0.16
Male (%)	73.7	67.4	77.4	0.44
Prehospital electrocardiogram done (%)	29.5	21.7	35.5	0.20
Self-transport (%)	35.8	41.3	29.0	0.34
Weekend arrival (%)	25.3	23.9	25.8	1.00
Nighttime arrival (%)	31.6	30.4	22.6	0.60
Onset to emergency department (min)*	289.5 ± 393	263.4 ± 375	340.7 ± 445	0.45
Door-to-balloon (min)	123.1 ± 61	133.5 ± 53	94.3 ± 37	<0.0001
Door-to-electrocardiogram (min)	10.7 ± 12	13.7 ± 14	5.7 ± 8	0.007
Death (%)	3.2	2.2	3.2	0.78

*data were available for 82 of the 95 patients.

HCIS, hospital care improvement strategies; SD, standard deviation. Continuous variables are expressed as mean \pm SD.

Table 2: Study outcomes

	Before HCIS (Mean \pm SD)	After HCIS (Mean \pm SD)	P value	Difference (Mean \pm SE)
Door-to-balloon (min)	133.5 ± 54	94.3 ± 37	<0.0001	39.2 ± 10
Door-to-electrocardiogram (min)	13.7 ± 14	5.7 ± 8	0.007	8.0 ± 3

HCIS, hospital care improvement strategies; SD, standard deviation; SE, standard error.

the patients before HCIS implementation (94.3 ± 37 minutes vs 133.5 ± 53 minutes; $P < 0.0001$; and 13.7 ± 14 vs 5.7 ± 8 ; $P = 0.007$, respectively).

Forty-eight patients met the criteria for the cardiac alert protocol; it was used in 25% of these patients; all of these arrived by emergency medical services. In patients for whom the cardiac alert was called, the door-to-balloon time and the door-to-ECG time was shorter than in patients that did not have the cardiac alert called (78.3 ± 18 minutes vs 124.8 ± 73 minutes; $P = 0.001$ and 4.7 ± 3 minutes vs 8.8 ± 11 minutes; $P = 0.05$, respectively).

Patients that had a cardiac alert called had a shorter time from symptom onset to ED (112.7 ± 75 minutes vs 392.5 ± 458 minutes; $P = 0.003$). Multivariate linear regression was used to account for the shorter symptom onset to ED presentation time. Onset to ED presentation time (as a continuous variable) and initiation of cardiac alert (as a categorical variable) were entered as simultaneous covariates for door-to-balloon time. Cardiac alert remained a significant predictor ($P = 0.029$) after controlling for the shorter symptom onset to ED presentation time.

Four patients who presented after the offhours catheterization laboratory was in place were compared with 17 patients presenting before. The door-to-balloon time was lower after implementation (78.8 ± 17 vs 118.5 ± 38 minutes), implicating a trend ($P = 0.057$).

Further univariate analysis showed emergency medical services transport and presence of prehospital ECG predictive of a reduced door-to-balloon time (mean \pm SE) by 38.8 ± 14 ($P = 0.009$) and 23.7 ± 12 ($P = 0.043$) minutes, respectively.

Lastly, a multivariate logistic regression model was constructed to determine the significant predictors of less delay (defined as submedian door-to-balloon time). Baseline variables (age and gender), timing variables (day/nighttime, weekday/weekend, and pre-/post-HCIS implementation) along with type of transport and whether or not a prehospital ECG was received were all entered as potential predictors into a backward stepwise regression equation. It was found that patients admitted after HCIS implementation (odds ratio [OR], 4.62; confidence interval [CI], 1.6–13.0; $P = 0.004$) and patients with a prehospital ECG (OR, 3.83; CI, 1.4–10.7; $P = 0.01$) were more likely to experience less delay.

DISCUSSION

After implementation of 3 hospital care improvement strategies (cardiac alert protocol, individualized feedback on treatment times and a 24-hour inhouse catheterization laboratory on weekdays, door-to-PCI time [mean \pm SE]) for patients with STEMI was reduced by 39.2 ± 10 minutes. The mean door-to-balloon time after initiation of HCIS was 94.3 ± 37 in this study, reducing it to less than the national median door-to-balloon time of 100 minutes (10) and within the 90 ± 30 -minute range advised by the American Heart Association/ American College of Cardiology (AHA/ACC) for facilities providing primary PCI as treatment of AMI (11).

Shorter door-to-balloon times were associated with implementation of the cardiac alert protocol (difference: 46 ± 13 minutes; $P < 0.001$) and a trend for improvement using 24-hour inhouse catheterization laboratory staffing (difference: 39.7 ± 20 minutes; $P = 0.057$). However, the cardiac alert was initiated in only 25% of the patients eligible. Increased utilization, also in patients not presenting by emergency medical services, may further improve times to treatment. Unfamiliarity of the ED physicians and cardiologists with the protocol, combined with the busy ED setting, may have contributed to this low-protocol implementation rate.

In patients presenting during weekday nights, the door-to-balloon time was shorter (78.8 ± 17 vs 118.4 ± 38 minutes) after 24-hour catheterization laboratory staffing was implemented; however, because of limited numbers in these groups, the difference was not statistically significant. Patients presenting at offhours with STEMI have been reported to have a longer door-to-balloon time (12). The National Registry of Myocardial Infarction reported an increment in nocturnal door-to-balloon time of 22 minutes (13); thus, the data trend seen in the current analysis supports the effectiveness of a 24-hour inhouse catheterization laboratory in preventing offhour delays.

Interestingly, the door-to-ECG time was reduced after implementation of HCIS (5.7 ± 8 vs 13.7 ± 14 minutes). The first of the 3 HCIS to be implemented was the cardiac alert. As part of the cardiac alert protocol, crosstraining was done of ED nurses in ECG acquisition; additionally, the ECG technicians were included in the paging list, explaining the shorter time in the patients for whom the cardiac alert was called. Overall heightened awareness among ECG personnel during implementation of the cardiac alert initiative may have attributed to the shorter door-to-ECG time also for patients for whom the cardiac alert was not called.

The effect of a shortened door-to-balloon time in patients with a prehospital ECG has been described previously; furthermore, it may improve the utilization of the HCIS described in this article; having a diagnostic prehospital ECG could improve implementation of the cardiac alert by reducing time to diagnosis (5). Additionally, implementation of a prehospital ECG transmission system to the cardiologist may prove effective in reducing time to treatment (14).

There were no statistically significant differences in mortality between the patient groups; however, the study was not powered to detect such differences. The study was designed and executed to evaluate the effectiveness of the in-hospital measures to reduce time to treatment, measured as door-to-balloon time.

Symptom onset-to-balloon time has been shown to be a better predictor of outcome than door-to-balloon time (1,2). Patient treatment delay is a difficult issue to address. In this population, the mean symptom onset-to-ED time was nearly 5 hours (289.5 ± 393 minutes), which may in part be attributed to demographic characteristics; the prevalence of diabetes in West Virginia is one of the highest in the nation (16), the associated atypi-

cal symptom presentation in diabetic patients may have contributed to the delay. The potential for reducing prehospital delays through patient/population education should be emphasized.

One limitation of this study is that it was a retrospective review; however, confounding factors, including age, mode of transportation, time of symptom onset, gender, and prehospital ECG, were taken into account. Nevertheless, there may have been other factors affecting the door-to-balloon times that were not accounted for in this study. The findings could be the result of the fact that the healthcare team was aware of changes being made to the treatment process. However, at the time of implementation, no knowledge existed that this research project would be conducted.

The patient group was limited, and because it only included patients with STEMI who received PCI treatment, the results are not applicable to non-STEMI patients. Furthermore, it was a single-center study; local patient characteristics, community health care facilities, and patient care practices limit the generalization of the results.

SUMMARY

Comprehensive HCIS, including a cardiac alert protocol, individualized feedback on cardiologist treatment times, and implementation of a 24-hour inhouse catheterization laboratory during weekdays, were effective in reducing door-to-balloon time by 39 minutes for patients with STEMI.

REFERENCES

1. De Luca G, Suryapranata H, Zijlstra F, et al. ZWOLLE Myocardial Infarction Study Group Symptom-onset-to-balloon time and mortality in patients with acute myocardial infarction treated by primary angioplasty. *J Am Coll Cardiol.* 2003;42:991–997.
2. De Luca G, Suryapranata H, Ottervanger JP, et al. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation.* 2004;109:1223–1225. Epub March 8, 2004.
3. Goff DC, Sellers DE, McGovern PG, et al. Knowledge of heart attack symptoms in a population survey in the United States: the REACT trial. Rapid early action for coronary treatment. *Arch Intern Med.* 1998;158:2329–2338.
4. Foster DB, Dufendach JH, Barkdoll CM, et al. Prehospital recognition of AMI using independent nurse/paramedic 12-lead ECG evaluation: impact on in-hospital times to thrombolysis in a rural community hospital. *Am J Emerg Med.* 1994;12:25–31.
5. Kereiakes DJ, Gibler WB, Martin LH, et al. Relative importance of emergency medical system transport and the prehospital electrocardiogram on reducing hospital time delay to therapy for acute myocardial infarction: a preliminary report from the Cincinnati Heart Project. *Am Heart J.* 1992;123:835–840.
6. Berglin Blohm M, Hartford M, Karlsson T, et al. Factors associated with pre-hospital and in-hospital delay time in acute myocardial infarction: a 6-year experience. *J Intern Med.* 1998;243:243–250.
7. Pell AC, Miller HC, Robertson CE, et al. Effect of 'fast track' admission for acute myocardial infarction on delay to thrombolysis. *BMJ.* 1992;304:83–87.

8. Coronary angioplasty: guidelines for good practice and training. Joint Working Group on Coronary Angioplasty of the British Cardiac Society and British Cardiovascular Intervention Society. *Heart*. 2000;83:224–235.
9. The Centers for Medicare & Medicaid Services web site. Available at: <http://www.cms.hhs.gov/>.
10. National Registry of Myocardial Infarction 5 Quarterly Data Report; Patients Discharged July 2003–June 2004, National Door to Dilatation Time for Non Transfer-In Patients.
11. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction). *J Am Coll Cardiol*. 2004;44:E1–E211.
12. Sadeghi HM, Grines CL, Chandra HR, et al. Magnitude and impact of treatment delays on weeknights and weekends in patients undergoing primary angioplasty for acute myocardial infarction (the Cadillac trial). *Am J Cardiol*. 2004;94:637–640.
13. Angeja BG, Gibson CM, Chin R, et al. Predictors of door-to-balloon delay in primary angioplasty. *Am J Cardiol*. 2002;89:1156–1161.
14. Lipton J, Young D, Sejersten M, et al. Pre-hospital ECG-transmission to shorten time to treatment in myocardial emergency. *J EMS*. In press.
15. Dracup K, Moser DK, Eisenberg M, et al. Causes of delay in seeking treatment for heart attack symptoms. *Soc Sci Med*. 1995;40:379–392.
16. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA*. 2003;289:76–79.

Part II

Alarm management in intensive cardiac care

Chapter 6

Alarms on the intensive cardiac care unit

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ABSTRACT

Patients admitted to the Intensive Cardiac Care Unit are closely monitored by different devices that generate alarms when an abnormality is detected. However, most alarms do not signify a life-threatening event. During a four month period 34,827 alarms were collected electronically. The most frequent alarm categories were related to mechanical ventilation (42.2%), blood pressure (32.3%), electrocardiogram (9.8%) and heart rate (8.1%). 2750 (7.9%) of the alarms were not related to limit violations, but were technical advisories. Overall alarm frequency was 2.2 per patient per hour. However, the distribution over time varied greatly and alarm “bursts” were seen when blood samples were taken and patients were woken. Reduction in alarms could be achieved by reducing overuse of monitoring parameters, utilizing patient specific limits and combining alarms within the “bursts”.

INTRODUCTION

Patients admitted to the Intensive Cardiac Care Unit (ICCU) are closely monitored by different devices. When an abnormality is detected, an alarm is generated. Alarms can be categorized as a limit violation or as an advisory message. Limit violations occur when a (physiological) parameter exceeds a pre-defined value (for example a high heart rate), advisory messages indicate a technical problem (for example a lead disconnection) or a medical situation requiring action (such as an empty syringe in an infusion pump). Alarms are further classified according to urgency (1). A high priority alarm indicates a critical situation requiring immediate response; medium priority indicates a dangerous situation requiring urgent, but not immediate response; low priority alarms require attention, but not immediately. Default alarm settings are set up by the manufacturer to maximize sensitivity, at the cost of a high false positive rate (2): most alarms do not signify a life-threatening event.

The reported frequency of alarms in the intensive care environment ranges from 1.6 (3) to 14.6 (4) per hour with a false alarm rate of up to 91% (5). Approaches to improving alarm accuracy have been described (6-8), however implementation is limited. Current patient care devices allow the electronic transmission of alarms to a central gateway (9) and may facilitate the implementation of certain strategies to improve alarm accuracy.

The aim of this study was to evaluate the distribution over time and by category of electronically collected alarms on the ICCU, and to describe how this information could be used to reduce frequency and improve the accuracy of alarms.

METHODS

From 17 December 2008 through 16 April 2009 alarms from the 8-bed ICCU at the Erasmus Medical Center, Rotterdam, Netherlands, were received from the patient monitoring network (9). The intelligent Patient Universal Tele Alarm (i-PUT) (10), an open source toolkit was used to collect the alarms from the network and store them in a SQL database for analysis (11).

Devices hooked up to the monitoring network included blood pressure, hemodynamic and oxygen saturation monitors as well as mechanical ventilators. Alarms generated by infusion and feeding pumps, dialysis and circulatory assist devices, air mattresses and other patient care devices were not analyzed as they were not hooked up to the monitoring gateway.

The alarms were categorized by type and urgency based on the information received from the gateway. The number of alarms was determined for each hour during the study period. The number of alarms was compared for: nighttime hours (0.00-6.00) vs. daytime, weekday vs. weekend and hours with extra activity vs. the other "normal" hours. Extra ac-

Acute tivity was present from 6.00-7.00, when patients were awakened and blood samples were drawn, and from 8.00-10.00 when patients were washed.

Student's t-test (SPSS version 12) was used to evaluate differences in hourly alarm rate between categories. Continuous data is displayed as mean \pm SD or median (IQR) as appropriate. A P-value of <0.05 was considered statistically significant.

RESULTS

Over the four month period 34,827 alarms were collected during 547 patient admissions with a duration of 6.1(3-23) hours.

The most frequent alarm categories are displayed in Table 1 and were related to mechanical ventilation (42.2%), blood pressure (32.3%), electrocardiogram (9.8%) and heart rate (8.1%). 2750 (7.9%) of the alarms were not limit violation alarms, but technical advisory messages. Main causes of these advisory messages were: ECG artifacts (64.9%), disconnected devices (29.3%) and SpO₂ artifacts (2.9%).

The median alarm frequency was 9 (5-18) for the ICCU per hour (on average 2.2 per patient per hour). The number of alarms per hour on the ICCU is displayed in Figure 1. There was overall decreased alarm frequency during night-time (0.00 until 6.00) when compared to day: 7 (3-13) vs. 11 (5-19) per hour ($P<0.001$).

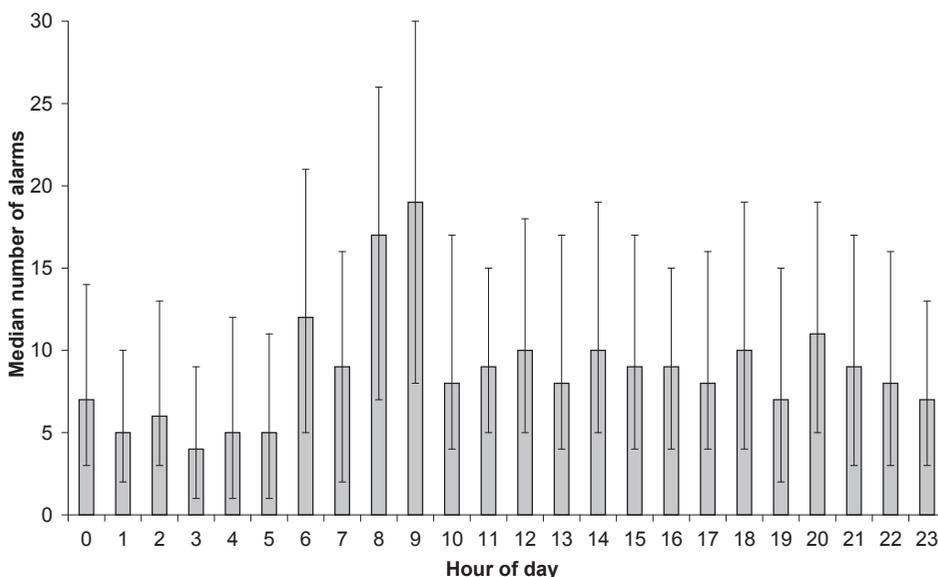


Figure 1: Median number of alarms on the intensive cardiac care unit per hour. Error bars indicate the interquartile range.

A peak in alarm frequency was seen at the time of drawing blood samples from the arterial line and awakening of the patients. Another peak occurred between 8.00 and 10.00 when patients are washed. The alarm frequency during these peaks was 17 (8-26) per hour vs. 9 (4-16) during other hours ($P < 0.001$). There was no difference in frequency of alarms by day of week.

Table 1: Distribution of alarms by type

Alarm type	%	n
Respiratory	41.2%	14,357
Blood pressure	32.3%	11,249
Electrocardiogram	9.8%	3,430
Heart rate	8.1%	2,822
Advisory	7.9%	2,750
Temperature	0.3%	121
Left atrial pressure	0.1%	49
O ₂ saturation	0.1%	49
Total	100%	34,827

The time between alarms varied greatly with a median of 1.3 (0.5-4.1) minutes, mainly due to the occurrence of alarm "bursts": in 50% of the alarms the interval was less than 90 seconds. The skewed distribution of the alarm intervals is apparent in the histogram in Figure 2: note that the time interval is a logarithmic scale.

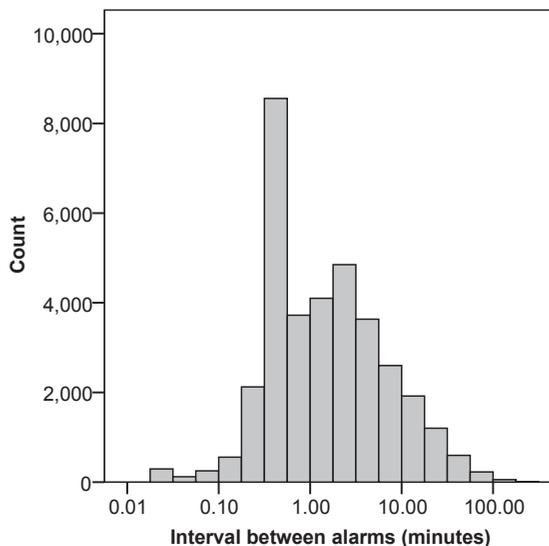


Figure 2: Histogram of the time inbetween alarms.

DISCUSSION

The current study evaluated frequency of alarms received electronically by a central gateway and included alarms generated by blood pressure, electrocardiogram, O₂ saturation and respiratory therapy patient care devices.

The mean daily number of alarms per bed in the current study was 37 ± 22 , which is similar to the 39 reported by Chambrin et al. (3) in a general intensive care unit. Additionally, they also reported a lower frequency during the night-time shift.

Siebig et al. (12) evaluated the differences in alarm distribution between the different intensive care units of the same hospital, and found them to be similar. They did not find a difference in alarm frequency related to time, and reported a higher rate of 4.3 alarms per patient per hour, even though they did not include respiratory alarms. Alarm settings, but also a different collection method (using a custom program to extract the alarms from the monitors) may explain the higher frequency.

The lower frequency of alarms during night-time in the current study may be due to less patient activity and less planned procedures. In the current study, the distribution of alarms over time varied greatly due to the occurrence of alarm "bursts". There are several explanations for this clustering.

First, in the case of a true critical event, many monitored parameters are likely to change simultaneously or sequentially within a short time period, as they are physiologically linked, and would generate alarms as their limits are violated. Second, in the case of a procedure, artifacts of different monitoring parameters may be generated within a short time period; the nurse may draw blood from the arterial line, generating several alarms from the invasive blood pressure monitor, and may suction the airway, causing respiratory alerts. Third, during the admission or discharge of a patient, many alarms are generated as the patient is hooked up to or disconnected from the different monitoring devices. Lastly, it can be expected that a random distribution of the events comes with a random, and thus unequal distribution over time.

To reduce the frequency and improve the accuracy of alarms, different strategies have been described. Most importantly, for each patient, the necessity of monitoring should be evaluated for each parameter, based on the patient specific risk profile (13).

Further, appropriate adjustment is needed for the limits of the parameter. Additionally, alarm settings should be dealt with appropriately before performing a procedure (6). User knowledge on how to do this is necessary, and may be aided by uniform interfaces on devices from different manufacturers. This could reduce the higher frequency of alarms seen during hours of blood drawing and patient washing.

Also, utilizing patient care device "intelligence" may improve the accuracy of the alarms. Different strategies have been described (7,14), and include the use of trends, combining information from different channels within the device, and automated setting of limits.

However, though these strategies are necessary to reduce the frequency and improve the accuracy, they may not be sufficient on their own.

In the future, the number of patient care devices is likely to increase, and to successfully implement intelligence, devices will need to have access to information obtained by other devices (eg. in the absence of a signal, an electrocardiographic monitor could send a disconnect alert rather than an asystole alarm if it knows that there is a heart rate detected by a different patient care device). Additionally, the alarm needs to be delivered to the appropriate caregiver. This concept becomes more important as patients are cared for in individual rooms, sometimes in isolation: audible alerts generated by a patient care device are only noticed when the caregiver is in the room.

The current study demonstrates that it is feasible to collect alarms electronically from different monitoring devices. I-PUT (10), the platform used, provides a starting point for reducing alarm frequency. First, it can be used to evaluate the effect on alarm frequency of user targeted interventions to improve utilization of monitoring and alarm limit settings. Second, i-PUT can be used to generate 'smart alarms'. Alarm data can be sent to a third party decision rule engine, such as GASTON (15). A clinician or nurse can then design decision rules using the alarms from i-PUT to aggregate and process information from multiple alarms into 'smart alarms'. Finally, i-PUT can provide output to different modalities, such as paging, but also SMS and web-based devices. Thus, different strategies can be applied to optimize the delivery of alarms to the caregiver.

LIMITATIONS

The current study evaluated alarms generated by patient care devices hooked up to a monitoring network. Other patient care devices such as infusion and feeding pumps, patient beds, dialysis and circulatory assist devices, and others may also be hooked up to a patient, and may contribute significantly to the alarm load. However, it is unlikely that the alarm trends from other devices are much different from the current analysis.

There may be a slight discrepancy between the audible alarms and the alarms collected in the current study; given certain circumstances, a device may generate an alarm to the gateway without producing an audible alert. The goal of the current study was to investigate how electronically collected information could help reduce the alarm frequency; however this issue needs to be addressed when implementing a solution.

The current study did not investigate the accuracy of the alarms. Previous studies in intensive care settings have shown that alarms in an intensive care setting have a low specificity (3-5,16). The occurrence of bursts related to hours of increased activity suggest that there may be more false positives during these periods. However, prospective evaluation is necessary to confirm this.

CONCLUSIONS

Alarms on the ICCU were unequally distributed over time: increased frequency was seen during hours with extra activity and during daytime.

Electronic collection of alarms is feasible, can facilitate the evaluation of user targeted interventions to reduce alarm frequency, and when combined with a rule-engine, could combine data from different monitoring devices to generate “smart alarms”.

REFERENCES

1. Collateral standard: general requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems. IEC/TRF 60601-1-8 - Ed. 3.0. IEC; 2006.
2. Quinn ML. Semipractical alarms: A parable. *Journal of Clinical Monitoring and Computing*. 1988 ;5(3):196-200.
3. Chambrin MC, Ravaux P, Calvelo-Aros D, Jaborska A, Chopin C, Boniface B. Multicentric study of monitoring alarms in the adult intensive care unit (ICU): a descriptive analysis. *Intensive Care Med*. 1999 Dec ;25(12):1360-1366.
4. Biot L, Carry P.Y.[1], Perdrix J.P., Eberhard A., Baconnier P. Clinical evaluation of alarm efficiency in intensive care unit. *Annales Francaises d'Anesthesie et de Reanimation*. 2000 Jun ;19459-466.
5. Koski EM, Mäkivirta A, Sukuvaara T, Kari A. Frequency and reliability of alarms in the monitoring of cardiac postoperative patients. *Int J Clin Monit Comput*. 1990 Apr ;7(2):129-133.
6. Görges M, Markewitz BA, Westenskow DR. Improving alarm performance in the medical intensive care unit using delays and clinical context. *Anesth. Analg*. 2009 May ;108(5):1546-1552.
7. Imhoff M, Kuhls S. Alarm Algorithms in Critical Care Monitoring. *Anesth Analg*. 2006 May 1;102(5):1525-1537.
8. Beneken JE, Van der Aa JJ. Alarms and their limits in monitoring. *J Clin Monit*. 1989 Jul ;5(3):205-210.
9. Nelwan S, Meij S, Fuchs K, van Dam T. Ubiquitous access to real-time patient monitoring data. In: *Computers in Cardiology 1997*. 1997. p. 271-274.
10. van Ettinger M. intelligent Patient Universal Tele-alarm [Internet]. [cited 2009 Aug 26] Available from: <http://sourceforge.net/projects/i-put/>
11. van Ettinger M, Lipton J, Fuchs K, van Dam T, van der Putten N, Nelwan S. An Open Source Toolkit for Managing Patient Monitoring Device Alarms Based on the IHE Alarm Communication Management Profile. *Computers in Cardiology 2009*.
12. Siebig S, Kuhls S, Gather U, Imhoff M, Müller T, Bein T, et al. Lärm auf der Intensivstation. *Der Anaesthesist*. 2009 Mar 1;58(3):240-246.
13. Chambrin MC. Alarms in the intensive care unit: how can the number of false alarms be reduced? *Crit Care*. 2001 Aug ;5(4):184-188.
14. Feldman JM, Ebrahim MH, Bar-Kana I. Robust sensor fusion improves heart rate estimation: clinical evaluation. *J Clin Monit*. 1997 Nov ;13(6):379-384.
15. de Clercq PA, Hasman A, Blom JA, Korsten HH. Design and implementation of a framework to support the development of clinical guidelines. *International Journal of Medical Informatics*. 2001 Dec ;64(2-3):285-318.
16. Tsien CL, Fackler JC. Poor prognosis for existing monitors in the intensive care unit. *Crit. Care Med*. 1997 Apr ;25(4):614-619.

Chapter 7

An open source toolkit for managing patient monitoring device alarms based on the IHE alarm communication management profile

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ABSTRACT

The “Integrating the Healthcare Enterprise” (IHE) initiative has defined an Alarm Communication Management (ACM) profile as part of the Patient Care Device (PCD) domain in order to communicate alarms from patient monitoring and therapeutic devices in a consistent way.

We have implemented an extensible, open source toolkit (C#) based on the ACM profile and interfaced our patient monitoring equipment (Dräger Medical), and infusion pumps (Alaris) using several export interfaces available in the intensive care units of the Erasmus MC.

In conclusion, an open source framework of the IHE PCD ACM profile was developed and provides a starting point for a centralized, uniformed approach to device alarm management. In the future devices could use alarms generated by other devices to decrease the number of false alarms.

The toolkit is available at: <http://i-put.sourceforge.net>

INTRODUCTION

At an Intensive Care Unit (ICU) a patient is connected to multiple types of Patient Care Devices (PCD). Alarms generated by PCDs can both be of physiological and technical nature. Figure 1 provides an overview of the common PCDs associated with a patient. Parameters typically monitored on the ICU include: ECG, blood pressure (invasive and non invasive), O2 saturation and temperature. Limit violations will trigger alarms, additionally advisory alarms are generated (for instance in the case of ECG lead disconnection). PCDs related to respiration, dialysis and other therapies may also be connected.

In the ICU, medications are frequently administered by infusion pumps which generate alarms when the medication becomes depleted or in the case of obstruction. The large number of monitored parameters and connected PCDs in an ICU can generate a high frequency of false-positive alarms (1). Patients themselves are also able to generate an alarm by pressing a patient alarm button. Although most PCDs generate very similar output for alarms, the devices are rarely integrated in a single system for alarm distribution.

Integrating the Healthcare Enterprise (IHE) (2) is an initiative started in 1997 by healthcare professionals and industry to improve the way computer systems in healthcare share information. In 2005 the IHE formed the IHE PCD domain to address the integration of medical devices with healthcare computer systems. The IHE PCD domain intends to improve flow of information between the point-of-care and the Electronic Healthcare Record (EHR). Work was started in 2008 on a profile for alarm management resulting in a draft for trial implementation: the Alarm Communication Management (ACM) profile (3). The ACM profile strives to establish interoperability between systems of different manufacturers and may result in a communication standard for alarm messages.

Our aim is to provide better insight into the generated alarms and to enable techniques for combining alarms from different PCDs: to do this a centralized system needs to serve as a gateway for alarms from different PCDs.



Figure 1: Patient Care Devices at the point of care (in the Intensive Care Unit)

METHODS

The ACM profile specifies four major elements: Alarm Source (AS), Alarm Manager (AM), Alarm Communicator (AC) and Alarm Query (AQ) (see Figure 2). The Alarm Manager is the central system that connects the three other elements.

After implementation of the central application (AM), as specified in the ACM profile, a suitable distribution mechanism for the now centrally received alarms needs to be chosen. In the draft of the trial implementation the suggested distribution mechanism (AM to AC) is based on e-mail, however more suitable distribution mechanisms are available to allow alarm distribution to the medical staff. The following solutions were considered: pager, mobile phone, Personal Digital Assistant (PDA) and Smartphone. Some solutions will be manufacturer specific others will use open standards or are public domain.

Table 1 provides an overview of the provided solutions and their associated technologies which include: paging, SMS, e-mail, RSS (4) and Instant Messaging.

Pager, mobile phone and Smartphone can be used to deliver alarms to the roaming clinical staff. When sending a SMS, a status report can be requested to provide information regarding the message delivery. However, implementing this solution would contribute significantly to the complexity of the system.

The use of a PDA is less desirable than a pager or mobile phone due to battery life limitations. On the upside a PDA can provide additional information for each alarm: The user could immediately review vital signs and ECG tracings of the patient that generated the alarm. A Smartphone combines the capabilities of PDAs and mobile phones. Development on this platform will most likely lead to a viable system for receiving alarms.

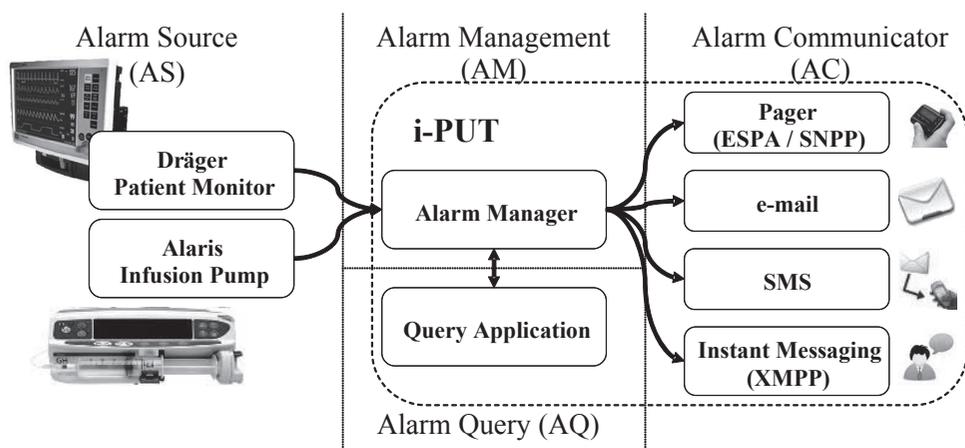


Figure 2: Overview of the intelligent Patient Universal Tele-alarm (i-PUT) toolkit and its integration at the Thoraxcenter. See text for the abbreviations.

RESULTS

We developed the intelligent Patient Universal Tele-alarm (5) (i-PUT), a toolkit that implements the ACM profile. The i-PUT toolkit (C#, ASP.NET and SQL) consists of three applications. The main application is the alarm manager, which can receive and distribute the alarms to configured disseminators: paging (ESPA (6) and SNPP (7) protocols), e-mail (specified in the ACM profile), SMS (based on GSMComm (8)) and instant messaging (XMPP protocol (9)). Additionally, the alarms can be stored into a SQL database.

The second application, AlarmQuery, enables a user to query for patient alarms. The third application, AlarmRSS, provides an RSS feed based on the database used by the alarm manager.

The alarm manager application can use multiple routes to distribute the received alarms and allows easy extension for the distribution channels using the plug-in architecture.

The i-PUT toolkit is available to the public in accordance with the Apache License Version 2.0 (10). An overview of i-PUT and its integration at our hospital is provided by Figure 2.

At our hospital we implemented two alarm source (AS) applications. These AS applications are integrated with commercial systems. After implementation of the AS applications the alarms could be distributed to the clinical staff.

To integrate the patient monitors we intercepted the alarm pages that are generated by the Infinity Gateway Suite (11). The Infinity Gateway provides an application to send alarms raised by patient monitors to a pager using a serial connection (ESPA). These pages were transformed to HL7 messages as specified in the ACM profile.

Finally, the infusion pumps were integrated. We used the XML interface provided by the Asena Gateway Workstation to retrieve the alarms. The retrieved data was transformed to HL7 messages as specified in the ACM profile. The XML interface of the Asena provides a very useful solution that allows the selection of a subset of the available information using eXtended Stylesheet Language Transformation (XSLT). Any changes in the selected data will then be send to the application over a TCP connection.

Table 1: Overview of systems and capabilities.

	Assured delivery	Confirmation	Pager	Mobile Phone	PDA	Smartphone	PC
Paging	X	X	X				
SMS	P			X		X	
e-mail	P			P	X	X	X
RSS				X	X	X	X
Instant Messaging		X			X	X	X

X, fully capable; P, partially capable.; PDA, Personal Digital Assistant; PC, Personal Computer; SMS, Short Message Service; RSS, Really Simple Syndication.

DISCUSSION

The open source toolkit, an implementation of the IHE PCD domain ACM profile, is a starting point for a centralized and uniform approach for alarm management.

PCDs on a single ICU are frequently from different manufacturers. The resulting differences for each type of device will be an additional obstacle to integrate the alarms into a single system.

The i-PUT Toolkit still needs testing with each manufacturer's implementation of the ACM profile. This process could be catalyzed by participation to an IHE Connectathon (2). The ACM profile suggests support for both HL7 version 2 and 3. i-PUT does not yet support HL7 version 3, which limits the interoperability.

The integration of the alarms generated by the patient monitors can be further improved by using TapeRec (12), an application that can provide waveforms and trends associated with an alarm. Waveforms and trend could then be provided to the relevant care provider attached to an alarm. Further, the integration of the alarms generated by respiration and, dialysis devices, and/or patient alarm buttons should be considered.

Patient monitoring and therapeutic devices at the bedside generate many audible and visual alarms, interrupting care by requiring a clinician to review each alarm. Few of the alarms actually represent life threatening events; most result from (slightly) abnormal values or artefacts. Alarms are often presented on different screens, use different sounds and visual effects. Also, to change specific alarm settings, each device needs to be configured separately. Finally, devices do not exchange alarm information with other devices of the same patient, so each device will generate its own stream of alarms. Thus, a single physiological event may trigger different alarms (time, message and/or level) for each attached device.

The application of the ACM profile can lead to systems which reduce the frequency and obtrusiveness, while improving the accuracy of these alarms. The i-PUT Toolkit forms a foundation for such new applications.

An additional advantage of integration of all alarms into a single central system is the ability to track and trace the generated alarms. This provides insight into the frequency and types of alarms. A first step was taken using the database to provide an overview of the alarms generated at the ICCU of the Thoraxcenter (13).

When implementing an ACM, especially when planning to distribute the alarms to clinical staff, one must consider the effect on patient care. Additional disturbance of the clinical staff by devices like a pager, phone and/or PDA need to be limited to instances when it is in the best interest of the patient. An increase of unnecessary alarms can lead to ignoring of alarms and potentially to a delay in patient assessment.

In addition to sending alarm data directly to the relevant care provider, other information, such as lab values and advice generated by clinical decision support systems could be considered as opportunities to improve efficiency and quality of care.

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REFERENCES

1. Chambrin MC, Ravoux P, Calvelo-Aros D, Jaborska A, Chopin C, Boniface B. Multicentric study of monitoring alarms in the adult intensive care unit (ICU): a descriptive analysis. *Intensive Care Med.* 1999 Dec;25(12):1360-6.
2. Integrating the Healthcare Enterprise: IHE.net Home. Available from: <http://www.ihe.net/>
3. Integrating the Healthcare Enterprise: PCD Profile Alarm Communication Management Wiki. Available from: <http://wiki.ihe.net/index.php?title=ACM>
4. Winer D. RSS 2.0 Specification. Available from: <http://cyber.law.harvard.edu/rss/rss.html>
5. van Ettinger MJB. intelligent Patient Universal Tele-alarm. Available from <http://i-put.sourceforge.net/>
6. On-Site Communications Association: PROPOSAL FOR SERIAL DATA INTERFACE FOR PAGING EQUIPMENT. 1984; Available from: <http://www.osca-uk.com/ESPA%20444.pdf>
7. Gwinn A. RFC 1861 (rfc1861) - Simple Network Paging Protocol - Version 3 -Two-Way E. 1995; Available from: <http://www.faqs.org/rfcs/rfc1861.html>
8. Mayr S. Sending short messages (SMS) via GSM mobile phones. Available from: <http://www.scampers.org/steve/sms/>
9. XMPP Standards Foundation. Available from: <http://xmpp.org/>
10. The Apache Software Foundation: Apache License Version 2.0. Available from: <http://www.apache.org/licenses/>
11. Nelwan SP, Meij S, Fuchs K, van Dam T. Ubiquitous access to real-time patient monitoring data. *Computers in Cardiology* 1997;24:271-4.
12. Nelwan SP, van Dam TB, Scholz W, Fuchs KJ, Demur C, de Wijs MCJ, van Ettinger MJB, van der Putten NHJJ. Evaluation of a Long-Term Continuous Full Disclosure Archiving System for Multi-Parameter Patient Monitoring Devices. *Computers in Cardiology* 2009;36.
13. JA Lipton, MJB van Ettinger, RJ Barendse, TB van Dam, NHJJ van der Putten, SP Nelwan. Frequency of Alarms on the Intensive Cardiac Care Unit. *Computers in Cardiology* 2009;36.

Chapter 8

Multimedia paging for clinical alarms on mobile platforms

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ABSTRACT

In the intensive care setting patient monitors generate many alarms. These alarms are frequently benign, but also unobserved as the caregiver is not at the location where the alarm is delivered. We developed a web-interface, integrated with an alarm manager that provides access to the “patient event” data. Alarm messages can be displayed by care unit and patient. Vital signs at the moment of the “patient event”, as well as before and after can be displayed. The interface is compatible with the main smartphone platforms (iPhone, Android, Blackberry, Windows Mobile and Symbian) and may facilitate a faster, more adequate response by caregivers to patient monitor alarms.

INTRODUCTION

Patients admitted to the Intensive Cardiac Care Unit are closely monitored and treated with different devices that generate alarms when an abnormality is detected. However, most alarms do not signify a life-threatening event. These alarms are typically provided by the patient care device, or at the central monitoring post at the nurse desk. However, caregivers are frequently away from either of these locations providing patient care or performing other tasks, and are not able to observe the alarms at all times. Additionally, default alarm settings are set up by the manufacturer to maximize sensitivity, at the cost of a high false positive rate (1): most alarms do not signify a life-threatening event. Delivery of patient care device alarms directly to the caregiver could result in faster, more adequate reaction to the messages. Solutions that provide this to pagers, and/or other portable devices, however are frequently limited to a single device manufacturer. In addition most pagers are only able to display (limited) amounts of text.

Many other portable electronic platforms exist and the choice is rapidly increasing with the popularity of the 'smartphone' and personal digital assistants (PDA). The clinical use of these devices is increasing, and many medical applications exist. However, these applications mainly provide disease specific information, and do not provide real-time patient specific data. Also, data is limited on the effectiveness of the use of portable electronic devices on patient care (2). The aim of the current project was to develop a technical, web-based, solution that allows delivery of "patient events" directly to the clinical staff on widely available mobile devices.

METHODS

The project was developed at the Thoraxcenter of the Erasmus Medical Center, Rotterdam, Netherlands. 78 beds over five care units are equipped with patient monitors. Each care unit is connected to a central gateway (3). Patient monitoring are automatically collected from the network and stored in a SQL database using the intelligent Patient Universal Tele Alarm framework (i-PUT) (4), an open source toolkit (5). Briefly, i-PUT uses ASP.NET 1.1, C#, SOAP and AJAX to collect and manage the alarms from the gateway.

Determination of primary requirements

First, we determined which data was valuable enough to present. To do this literature review and consultation of physicians and critical care nurses was done. Key questions were: Which clinical and non-clinical data needs to be directly displayed with a patient alarm? Which clinical data needs to be accessible to asses if the alarm requires further attention? How should alarms from different patients and care-units be displayed?

Determination of general system requirements

The user interface needed to be straight-forward and consistent. The system was not permitted to cause fatal errors on any of the devices the system was used on. When displaying an alarm, the system needed to provide accurate information, applicable to the alarm and the patient that it originated from. The system was intended as an enhancement, and not a replacement for the alarms generated by patient care devices.

Web interface requirements

The web-based interface needed to be accessible on various mobile devices. An overview of the different devices is given in Table 1. For the final design we chose to use a combination of HTML, Java-Script and server side generated PNG-images.

The system needed to provide access to recent alarms. To access each specific alarm the system needed to provide a list of all multimedia pages.

RESULTS

Taking these requirements into account, the system was developed over a period of 6 months. We developed a web-interface, integrated with an alarm manager that provides access to the "patient event" data. An overview of the system is given in Figure 1.

To achieve this data was accessed from TapeRec (3), a system that stores patient moni-

Table 1: Overview of smartphone platforms

	iPhone OS	Android OS	Windows Mobile	BlackBerry	Symbian OS
Resolution	480x320	480x800	480x800	480x360	640x360
WIFI / 3G	V / V	V / V	V / V	V / V	V / V
HTML	V	V	V	V	V
JavaScript	V	V	V	V	V
Java applet	-	-	V	-	-
Flash	-	-	V	V	V
SDK	Objective C	Java ME	.NET	Java ME	Java ME
Models investigated	iPhone 3G, iPod touch	Nexus One, G1	HTC HD2, HTC Touch2, Samsung B7610	Curve 8900, Tour 9630, Bold 9700	Nokia 5230, Nokia E71

Table 2: Overview of tested devices

	iPhone OS	Android OS	Windows Mobile	Black Berry	Symbian OS
Tested device	iPhone 3G	G1	Samsung B7610	Emulator	Nokia E71
Alarm list	V	V	V	V	V
Scroll list	V	V	V	-	-
Care Unit navigation	V	V	V	V	V
Bed specific	V	V	V	V	V
Show waveforms	V	V	V	V	V
Navigate waveforms	V	V	V	-	V
Scroll waveforms	V	V	-	-	-

toring data including vital signs and signal curves up to 72 hours for all admitted patients. Thus we were able to display the vital signs at the moment of the “patient event”, as well as the vital sign signals from 5 seconds before until 5 seconds after the “patient event”. The exact times are configurable.

The interface can be configured to display alarms for each patient bed or for an entire care unit and is updated every 5 seconds with new alarms (also configurable). By clicking (or touching when supported by the device) on an alarm, the message and vital signs displayed by the monitor at the moment of the alarm, enabling the user to make an informed decision regarding further action.

The system also provides a mechanism to add additional messages. Messages that could be included in the system are messages from patient care devices not attached to the monitoring gateway, the arrival of new lab result, or from a clinical decision support system.

To deliver the alarms that are provided by the web-interface directly to the caregiver, it needs to be accessible from, preferably, a mobile device. We tested the interface on a number of different platforms, including Smartphones. An overview of the main types is given in Table 2. The I-phone and Android platforms were able to display all of the web-interface features; Windows mobile 6.5 and Symbian were able to display the essential features; the feature of viewing vital sign tracings before and after the event was limited on the Blackberry to those at the moment of the actual alarm.

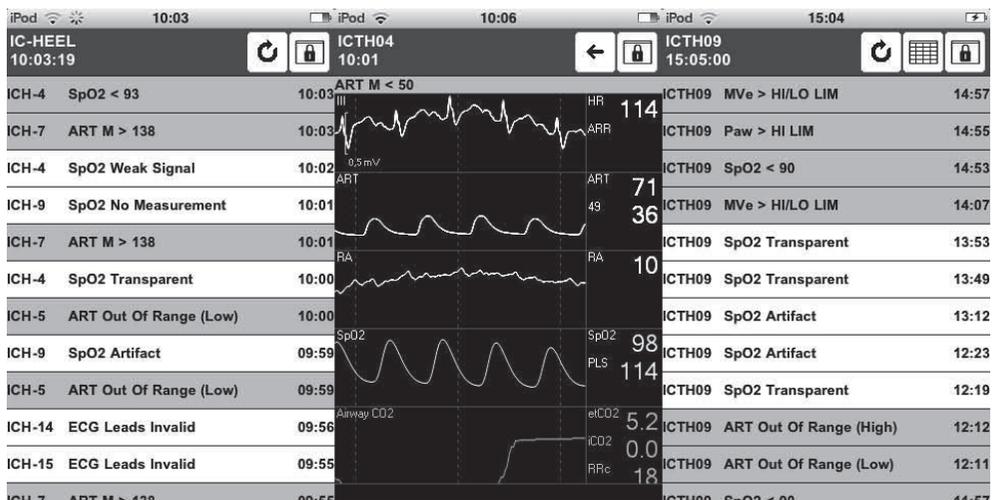


Figure 1. Example of multimedia paging interface. The severity of the alarm indicated by the background color. The left panel shows the alarms for a care unit, the center panel displays the vital signs at the moment of an alarm, the right panel displays all alarms for a patient bed.

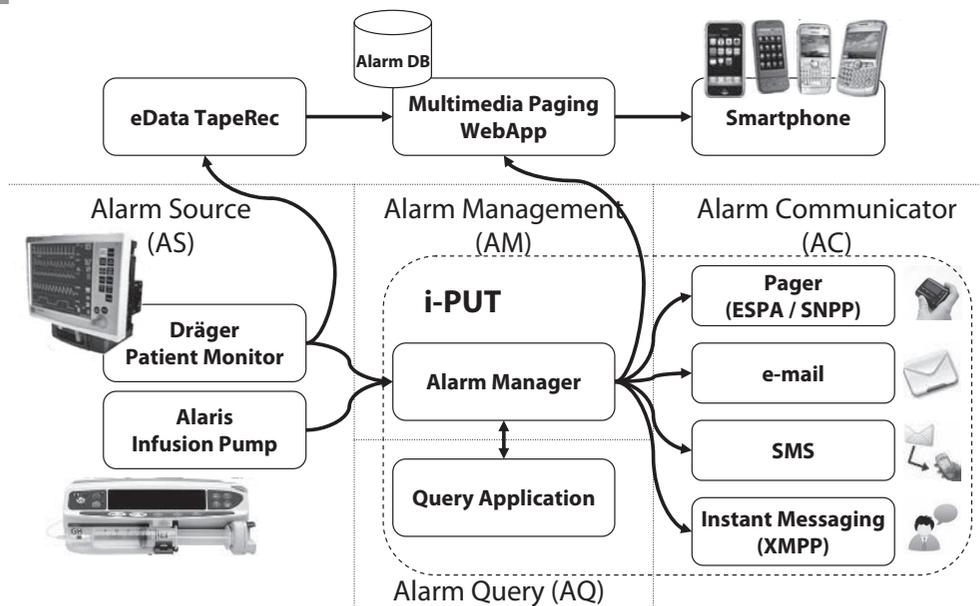


Figure 2: Overview of the intelligent Patient Universal Tele-alarm (i-PUT) toolkit and its integration at the Thoraxcenter. The ACM profile specifies four major elements: Alarm Source (AS), Alarm Manager (AM), Alarm Communicator (AC) and Alarm Query (AQ). The Alarm Manager is the central system that connects the three other elements.

DISCUSSION

We developed a multimedia paging application to allow delivery of alarms and clinical data directly to the caregiver on a portable electronic device.

Many manufactures of patient care devices also provide output of the alarms to different modalities. Paging devices are widely accepted and in use in most hospitals. However, they are limited in their ability to display information (limited number of characters and inability to display graphics). Increasingly, manufacturers are providing output to other modalities, including PDA's, sometimes using web-based technology. These solutions however are limited to a single manufacturer, and not yet widely in use. The current system, on the other hand, is expandable to other devices from different manufacturers, and provides support for multiple mobile platforms.

Applications are available that provide continuous access to patient monitoring data, however they are not event triggered, requiring continuous attention of the caregiver (6). These applications could be a useful add-on to the current system, enabling access to real time data in the case of an alarm.

Future development of smartphone and PDA based applications that allow access to clinical systems is likely to be difficult; currently different manufacturers provide their own platforms. Thus to provide access to the same clinical system from different smartphone devices, different versions of the application need to be developed for each device, inevitably leading to an unsupportable system. Two possible solutions to this problem exist. First, to choose one device for the application. This would however, lead to a restriction in the applicability of the application in different hospitals, or even over different departments. In certain environments there might be reasons to choose a different device, also availability may differ in different countries. In a 'worst case' scenario this would lead to the care provider carrying a number of different devices for different systems.

We propose a different approach: use of uniform web-based technologies to develop these applications. Most current, and all new smartphone and PDA devices support a subset of the standard the web technologies (HTML, Java-Script). A joint support of more powerful web-based technologies (HTML5, Java and/or Flash) by the device manufacturers would be an important step forward. Whether this would be achieved by implementing current technology (e.g. Java or Flash) or a new technology (still to be developed) is irrelevant, but it should be tackled jointly by all Smartphone manufacturers.

A further development of standards for patient monitoring device communication is needed to ensure reliable and complete exchange of vital patient information in between devices from different manufacturers (4,7).

Clinical evaluation of the system is needed to determine the effect on patient care: does delivery of critical alarms to the caregiver on a mobile device lead to a faster and more appropriate response? Also work is needed to enable the system to display new laboratory results, or CDSS results (for example an automated insulin protocol (8)). Other improvements might be viewing the patient directly via webcam, supplying trends in clinical data over a prior time period and provide access to clinical charting data.

An advantage of the current system is that evaluation of its use is possible using the alarm database; thus the effect of user targeted interventions to reduce alarm frequency can be evaluated. When combined with a rule-engine, "smart alarms" could be generated that utilize data from different monitoring devices, laboratory results and/or decision support messages. A different advantage of using a smartphone platform is that it could also be used by caregivers to communicate with each other.

A limitation of the current architecture is the need for network access, during initial testing there were many WiFi "dead-spots". A solution would be improved wifi access, or use of a different network type (UMTS). Due to this limitation it is important to have the existing patient monitors active, to ensure that the alarms are displayed even when they are not

Acute delivered to the mobile device. A further limitation is that the current system only provides one-way communication. Technically it would be possible to silence alarms from the mobile device, also the smartphone platform could enable the care-giver to talk directly to the patient. Future work is needed to investigate the feasibility of these enhancements.

A demonstration of the capabilities of the current system can be viewed at:
<http://www.spotchecker.eu/>

CONCLUSIONS

We developed a web based interface to display patient care device alarm messages and provide access to vital patient data at and around the time of the alarm. Alarm messages can be displayed by care unit and by patient. The interface is compatible with the main mobile device platforms and may facilitate a faster, more adequate response by caregivers to patient monitor alarms.

REFERENCES

1. Quinn ML. Semipractical alarms: A parable. *Journal of Clinical Monitoring and Computing*. 1988;5(3):196-200.
2. Prgomet M, Georgiou A, Westbrook JI. The impact of mobile handheld technology on hospital physicians' work practices and patient care: a systematic review. *J Am Med Inform Assoc*. 2009 Dec;16(6):792-801.
3. Nelwan S, Meij S, Fuchs K, van Dam T. Ubiquitous access to real-time patient monitoring data. In: *Computers in Cardiology 1997*. 1997. p. 271-274.
4. van Ettinger M, Lipton J, Fuchs K, van Dam T, van der Putten N, Nelwan S. An Open Source Toolkit for Managing Patient Monitoring Device Alarms Based on the IHE Alarm Communication Management Profile. *Computers in Cardiology 2009*.
5. van Ettinger M. intelligent Patient Universal Tele-alarm [Internet]. [cited 2009 Aug 26]; Available from: <http://sourceforge.net/projects/i-put/>
6. Nelwan S, Dam TV, Klootwijk, P, SH Meij. Ubiquitous Mobile Access to Real-time Patient Monitoring Data. *Computers in cardiology 2002*. 29:557-560.
7. Integrating the Healthcare Enterprise: PCD Profile Alarm Communication Management Wiki. Available from: <http://wiki.ihe.net/index.php?title=ACM>.
8. Barendse R, Lipton J, van Ettinger M, Nelwan S, van der Putten N. Implementing a Clinical Decision Support System for Glucose Control for the Intensive Cardiac Care [Internet]. In: *Artificial Intelligence in Medicine*. 2009 [cited 2009 Sep 30]. p. 161-165. Available from: http://dx.doi.org/10.1007/978-3-642-02976-9_21

Part III

Glucose regulation and outcomes

Chapter 9

The role of insulin therapy and glucose normalization
in patients with acute coronary syndrome

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Netherlands Heart Journal; in press

ABSTRACT

Patients with acute myocardial infarction (AMI) and diabetes mellitus, as well as patients admitted with elevated blood glucose without known diabetes, have impaired outcome. Therefore intensive glucose lowering therapy with insulin (IGL) has been proposed in diabetic- or hyperglycemic patients and has been shown to improve survival and reduce incidence of adverse events. The current manuscript provides an overview of randomized controlled trials investigating the effect of IGL. Furthermore systematic glucose-insulin-potassium infusion (GIK) has been studied to improve outcome after AMI. In spite of positive findings in some early studies, GIK did not show any beneficial effects in recent clinical trials and thus this concept has been abandoned. While IGL targeted to achieve normoglycemia improves outcome in patients with AMI, achievement of glucose regulation is difficult and carries the risk of hypoglycemia. More research is needed to determine the optimal glucose target levels in AMI and to investigate whether computerized glucose protocols and continuous glucose sensors can improve safety and efficacy of IGL.

INTRODUCTION

Diabetes is common in patients presenting with an Acute Coronary Syndrome (ACS). Furthermore, hyperglycaemia or impaired glucose tolerance is present in more than a third of ACS patients without known diabetes (1). Both in patients with diabetes as well as in nondiabetics with evolving myocardial infarction (AMI) hyperglycemia is associated with increased in-hospital death (RR 1.7 [1.2-2.4]), and with other adverse events including cardiac arrest, cardiogenic shock and pulmonary edema (2-4). Also in patients with stable coronary artery disease diabetes is associated with a higher 1-year incidence of death and cardiovascular events (13.0% vs. 5.6%) (5).

Hyperglycemia has been recognized both as mediator and as marker of adverse outcomes in ACS patients. Elevated glucose levels can reflect the severity of disease when it results from elevated catecholamine and cortisol levels. Also, the presence of additional conditions such as infection or sepsis may further disturb carbohydrate metabolism and glucose levels. Insulin resistance due to pre-existent diabetes (recognized or unrecognized) amplifies the stress related effects on glucose levels. In patients with AMI hyperglycemia is associated with higher free fatty acid concentrations (6), insulin resistance and impaired myocardial glucose metabolism, resulting in an increased oxygen consumption and consequently a more severe ischemic state (7). Insulin limits the detrimental effects of hyperglycemia by reducing glucose levels. Also, insulin may improve myocardial glucose utilisation by reducing free fatty acid concentrations due to its inhibitory effect on lipolysis (7). Finally, insulin has antithrombotic, anti-inflammatory and vasodilative properties (8-10).

In critically ill patients insulin therapy improves outcome (11-13). Also in hyperglycaemic patients with AMI glucose lowering insulin therapy is associated with reduced mortality at 7 and 30 days when compared to standard treatment (11.6 and 15.8% vs. 16.5 and 22.1%, respectively) (14). Similarly, in patients with stable coronary disease treatment of hyperglycemia is associated with a reduction in cardiovascular events at one year (HR 0.22 [0.05-0.97]) (15). The results of these observational studies have led to three randomized controlled trials investigating the effect of intensive glucose lowering insulin therapy (IGL) on outcomes in hyperglycaemic diabetic, and non-diabetic patients admitted with AMI (11,16,17).

A different concept of insulin treatment in ACS was tested in the form of a glucose-insulin-potassium infusion (GIK). This treatment was developed as a "polarizing solution" to prevent arrhythmias and avoid further ischemic damage in unselected patients with acute myocardial infarction (18,19). From 1960 onwards, different (randomized) trials have been done, utilizing GIK infusion and later insulin therapy in ACS patients.

The purpose of this manuscript is to provide an overview of the evidence for implementing IGL or GIK in ACS patients by comparing trials with regard patient characteristics, reperfusion treatment, study protocols and outcomes.

METHODS

A systematic PUBMED search was performed to identify all clinical trials with insulin (both IGL and GIK were included) in patients with unstable angina or AMI. MeSH terms used were "Myocardial Infarction", "Angina, unstable", "Insulin" and "Glucose". All abstracts were screened; when fitting the criteria the manuscript was obtained and reviewed. Other studies were included through references. Hazard ratios and confidence intervals for short-term mortality were recalculated to facilitate comparisons.

RESULTS AND DISCUSSION

The initial query gave 356 hits. After screening, 20 GIK and three IGL trials were reviewed. For the GIK studies performed before 1994, a review article was selected that provided a thorough analysis of these trials. From 1994 through 2004, 6 GIK trials were published that included patients with AMI or unstable angina. These differed from the prior studies in that patients included received reperfusion therapy. The three IGL studies are discussed separately and in more detail as they are more relevant to current clinical practice. An overview of the study characteristics is given in table 1. Outcomes and glycemic parameters are provided in table 2.

Glucose normalization

In the pre-thrombolytic era, two observational studies using historical controls, showed inconsistent results for the beneficial effect of insulin treatment in diabetic AMI patients. Clark et al. reported a reduced incidence of arrhythmias and death in the patients treated with IGL (20). In contrast, Gwilt et al. did not find a difference in mortality in diabetics treated with an insulin infusion protocol, though they did find a higher mortality rate in diabetic vs. non-diabetic AMI patients (21).

Between 1990 and 2004 three randomized controlled trials were performed including patients with AMI and known diabetes or hyperglycemia at admission (11,16,17). Patients from Europe (11,16) and Australia (17) were included; study size varied from 240 to 1253 patients. IGL was administered via an intravenous insulin regime for at least 24 hours to achieve glucose levels of <10.0 mmol/L. The DIGAMI studies included a 3 month subcutaneous insulin regimen as well. Admission glucose levels ranged from 10.8 to 15.7. At 24 hours glucose levels were reduced in both IGL and control groups, but more so in the IGL

Table 1: Overview of randomized controlled trials.

Study name	Inclusion	%PCI/thrombolysis/cabg/none	Location	Period
Fath et al.	Metaanalysis of 9 RCT's implementing GIK in AMI	0 / 1 / 0 / 99	Multi-center, international	1965 - 1987
Pol-GIK	Chest pain and ECG changes <24hours, IDDM excluded	0 / 60 / 0 / 40	Multi-center (16), Poland	1994 - 1995
Krjanac et al.	STEMI patients	0 / 100 / 0 / 0	Belgrade, Serbia	2000 - 2001
GIPS I	AMI presenting within 24 h of symptom	91 / 0 / 4 / 5	Zwolle, Netherlands	1998 - 2001
GIPS II	STEMI <24 hours, heart failure excluded	93 / 2 / 0 / 5	Multi-center (7), The Netherlands	2003 - 2004
Create-ECLA	STEMI presenting within 12 h of symptom onset	9 / 74 / 0 / 7	Multi center (470), international (>10)	1998 - 2004
OASIS 6	STEMI presenting within 24 hours (later 12 hours)	31 / 45 / 0 / 24	Multi-center (447) international (41)	2003 - 2004
DIGAMI I	AMI <24 hours and diabetes or glucose of > 11,0 mmol/L	0 / 50 / 0 / 50	Multi center (19), Sweden	1990 - 1993
DIGAMI II	AMI <24 hours, type 2 diabetes or >11,0 mmol/L	42 / 36 / 0 / 22	Multi center (44) International (6, Europe)	1998 - 2003
HI-5	AMI <24 hours with diabetes or >7,8 mmol/L	35 / 32 / 0 / 33	Multi center (6) Australia	2001 - 2004

RCT, Randomized Controlled Trial; IDDM, Insulin Dependent Diabetes Mellitus; AMI, Acute Myocardial Infarction; STEMI, ST-Elevation Myocardial Infarction; GIK, Glucose-Insulin-Potassium infusion; ECG, electrocardiogram.

Table 2: Study outcomes and glycemic parameters

Study	Treatment	Patients	Glucose target range (mmol/L)	Glucose level (mmol/L) admission	16-24 hours	Mortality (%) 30-40 days	HR (95% CI)	P	Long term mortality %	P
Fath et al.	control	972				21				
	GIK	956				16	0.76 (0.6 – 0.9)	0.004	-	
Pol-GIK	Control	460	-	7	6.2	4.8			6.5	
	GIK	494	< 16.8	6.9	5.9	8.9	1.85 (1.1 – 3.1)	0.01	11.1	0.01
Krijanac et al.	Control	40	-			10.0†			4.0	
	GIK	78	-			3.0†	0.30 (0.0 – 1.4)	0.08	10.0	0.18
GIPS-I	Control	464	-	8.5	8.1	5.8			8.2	
	GIK	476	7.0 – 11.0	8.5	7.7	4.8	0.83 (0.5 – 1.4)	0.50	6.5	0.32
GIPS-II	Control	445	-	8.3 ± 2.5	-	1.8			3.9	
	GIK	444	-	8.5 ± 2.8	-	2.9	1.61 (0.7 – 3.8)	0.27	5.3	0.33
Create-ECLA	Control	10107	-	9.0	7.5	9.7			-	
	GIK	10088	-	9.0	8.6	10	1.03 (0.9 – 1.1)	0.45	-	
OASIS 6	Control	1374	-			6.7			10.4	
	GIK	1374	-			7.6	1.13 (0.9 – 1.5)	0.36	10.8	NS
DIGAMI I	Control	314		15.7 ± 4.2	11.7 ± 4.1	15.6			26.1	
	Insulin 24h + 3 months SC	306	7.0 – 10	15.4 ± 4.1	9.6 ± 3.3	12.4	0.79 (0.5 – 1.2)	NS	18.6	0.027
DIGAMI II	Standard practice	306		12.9 ± 4.6	10.0 ± 3.6	7.5			17	
	Insulin 24h + 3 months SC	474	7.0 – 10.0 + fasting 5.0 – 7.0	12.8 ± 4.5	9.1 ± 3.0	7.5	1.00 (0.6 – 1.7)	NS	15	
HI-5	Insulin 24h	473	7.0 – 10.0	12.5 ± 4.4	9.1 ± 2.8	7.5	1.00 (0.6 – 1.6)	NS	12	NS
	Control	114		11.1 ± 3.5	9.0 ± 2.8*	7.1†			7.9	
	Insuline/dextrose	126	4.0 – 10.0	10.8 ± 4.1	8.3 ± 2.2*	4.4†	0.62 (0.2 – 1.8)	0.42	6.1	0.62

* mean glucose over 24 hours; † cardiac mortality; ‡ mortality at 3 months. HR, Hazard Ratio; CI, Confidence Interval; NS, Not statistically significant; GIK, glucose insulin potassium; SC, subcutaneous insulin. Glucose values are displayed as mean ± Standard Deviation.

groups. The difference in glucose levels between patients allocated to IGL or none ranged from 2.1 mmol/l (DIGAMI-1) to 0.7 mmol/L (the average over 24 hours in Hi-5). Long term mortality was lower in 2 of the 3 studies, but this was statistically significant in DIGAMI-1 only. However mortality was lower in the control group of DIGAMI-2.

DIGAMI-1 (11) was the first randomized trial for IGL, and showed a 29% relative reduction (18.6 vs. 26.1%) in 1-year mortality among hyperglycemic or diabetic AMI patients treated with IGL during the first 12 hours and continued subcutaneously for 3 months. Interestingly, about half of this difference in mortality was achieved in the first 3-months, while additional benefit occurred at longer follow-up. In this trial about half of the patients received thrombolytic therapy. The target for IGL in DIGAMI was a glucose level of 7 – 10 mmol/l.

The second DIGAMI (16) trial was designed to verify whether normalization of serum glucose (target 5 - 7 mmol/l for fasting glucose) would further improve outcome. Three treatment regimens were compared: IGL 24 hours, IGL 24 hours continued 3 months subcutaneously and a control group. No significant difference was seen in survival in the IGL groups compared to conventional management ($P = 0.203$) while, unexpectedly, the highest survival rate was observed in the control group.

The discrepancy between the first and second DIGAMI can be attributed to several factors. Most importantly, patients were less sick and admission glucose levels in DIGAMI-2 were lower than in DIGAMI-1 and the investigators did not succeed to normalize glucose levels in the IGL groups. The difference in glucose levels vs. controls was 2.1 mmol/l in DIGAMI-1 and only 0.9 mmol/l in DIGAMI-2. Additionally, in DIGAMI-2, 14% of the patients in the control group also received insulin infusion during hospital admission and the overall. Reperfusion treatment was given more often (78 vs. 50%).

The more recent HI-5 trial (17) did find a lower mortality at 3 and 6 months in favor of IGL, which is consistent with DIGAMI-1, although this was not statistically significant. There was also a lower incidence of heart failure during admission (12.7 vs. 22.8%; $P=0.04$) and reinfarction within 3 months (2.4 vs. 6.1%; $P=0.05$) in the insulin treated group. The mortality rates in the Hi-5 study were markedly lower than those in the DIGAMI studies. This can be explained by the younger population (62 vs. 68 years), by inclusion of non-diabetic subjects (48%), increased use of reperfusion therapy (67 vs. 50%) and overall improved care in the more recent time period (2001 - 2004 vs. 1990 - 1993) of the Hi-5 vs. the DIGAMI study.

Glucose target range and hypoglycemia

The results of DIGAMI-2 illustrate the difficulty in regulating glucose levels and achieving "optimal" target ranges. DIGAMI started insulin infusion in patients with a glucose level

of 11 mmol/l or higher, and aimed for values between 7 to 10 mmol/l. After the landmark trial from Leuven (22) in an intensive care population found a 10.4% absolute difference in mortality in favor of IGL targeted to 4.4 - 6.1 mmol/l, many subsequent trials used similar targets. However the latter trials were unable to reproduce the results (23). The most recent NICE-SUGAR trial, even reported a higher incidence of death, similar to DIGAMI-2. Since hypoglycemic episodes occurred more frequently in the IGL group, this resulted in a modification in the ACC/AHA guidelines (24) to use 10mmol/l as a threshold for initiating treatment in STEMI patients. The ESC guidelines (25) still mention a target range of 5 to 7.8 mmol/l, however these were established before the NICE-SUGAR results.

The fear for hypoglycemia in certain IGL protocols seems grounded, and prevention requires frequent measurement or a wider glucose target range. Meijering et al.(26) evaluated insulin protocols in 24 studies (including 6 with AMI patients). The best results were found using a dynamic scale protocol for continuous intravenous insulin infusion, combined with frequent blood glucose measurement and taking into account changes in glucose levels rather than single values.

Compliance with any glucose protocol is difficult to achieve. Computerized glucose protocols exist (27-29) and can improve protocol compliance and glycemic regulation; however frequent measurements are required. More recently a closed loop system for glycemic regulation in the intensive care unit has been developed using a continuous glucose sensor (30). This, however, requires further testing. Also, the reliability of continuous glucose sensors needs further improvement (31) and validation is necessary in the AMI patient population, particularly in patients with heart failure and hypo perfusion of the skin and subcutaneous tissues.

Glucose-insulin-potassium therapy

A meta-analysis by Fath et al. (32) of GIK trials done in the pre-reperfusion therapy era (before 1988) showed a lower mortality in the GIK treated group than in controls (16% vs. 21%; $P=0.004$). However, in later trials that included patients receiving reperfusion therapy (either by thrombolysis or mechanical), GIK did not show beneficial effects. The early randomized trials which were performed between 1994 and 2004 varied in size from 118 (33) to 20195 (34) and included patients in Europe (33,35,36) and other continents (37,38). Reperfusion therapy was given as thrombolysis or primary percutaneous coronary intervention (PCI) in less than 1% (32) to 100% of patients enrolled (33). Admission glucose values, when reported, varied from 6.9 to 9 mmol/l and were similar across control and GIK groups. All cause mortality at 30-40 days was higher in the GIK group in 4 of the 6 studies (reaching statistical significance in Pol-GIK). In three studies that reported longer follow up (6-12 months) the mortality difference in favor of the control group remained (also reaching statistical significance in Pol-GIK). Two studies showed a trend in cardiac

(Krljanac et al.) and all cause (GIPS) mortality in favor of GIK, though these did not reach statistical significance. Because in GIPS a subgroup of patients without heart failure had a lower 30-day mortality in the GIK treated group (1.2% vs. 4.2%, $P=0.01$) GIPS-2 was set-up excluding patients with symptoms of heart failure, but this study did not show any beneficial effect of GIK (35).

The differences in effect of GIK between the earlier and more recent studies can be explained by improvements in treatment (including reperfusion, antiplatelet and β -blocker therapy), which is reflected in the lower mortality rates of the studies performed after 1987. In the more recent studies all 30-40 day mortality rates were below 16%, which is the mortality rate of GIK-treated patients in the meta-analysis of trials from 1965 to 1987.

A parallel could be drawn from GIK to the administration of intravenous magnesium in AMI patients; promising beneficial effects in smaller studies were not confirmed in the large randomized MAGIC trial and the concept was abandoned (39).

CONCLUSION

Insulin treatment in AMI patients has been investigated extensively. The concept of systematic GIK in patients with elevated or normal glucose levels was not supported by recent trials in the reperfusion era, and has been abandoned.

IGL targeted to achieve normoglycemia can improve survival and reduce incidence of adverse events. However, achievement of glucose regulation is difficult and carries the risk of hypoglycemia. More research is needed to investigate the role of computerized glucose protocols and continuous glucose sensors to improve safety and efficacy of IGL.

REFERENCES

1. Rydén L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer M, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur. Heart J.* 2007 Jan;28(1):88-136.
2. Beck JA, Meisinger C, Heier M, Kuch B, Hörmann A, Greschik C, et al. Effect of Blood Glucose Concentrations on Admission in Non-Diabetic Versus Diabetic Patients With First Acute Myocardial Infarction on Short- and Long-Term Mortality (from the MONICA/KORA Augsburg Myocardial Infarction Registry). *The American Journal of Cardiology.* 2009 Dec 15;104(12):1607-1612.
3. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *The Lancet.* 2000 Mar 4;355(9206):773-778.
4. Norhammar A, Tenerz Å, Nilsson G, Hamsten A, Efendic S, Rydén L, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *The Lancet.* 2002 Jun 22;359(9324):2140-2144.
5. Lenzen M, Ryden L, Ohrvik J, Bartnik M, Malmberg K, Scholte Op Reimer W, et al. Diabetes known or newly detected, but not impaired glucose regulation, has a negative influence on 1-year outcome in patients with coronary artery disease: a report from the Euro Heart Survey on diabetes and the heart. *Eur. Heart J.* 2006 Dec;27(24):2969-2974.

6. Tansey MJ, Opie LH. Relation between plasma free fatty acids and arrhythmias within the first twelve hours of acute myocardial infarction. *Lancet*. 1983 Aug 20;2(8347):419-422.
7. Oliver MF. Metabolic causes and prevention of ventricular fibrillation during acute coronary syndromes. *Am. J. Med.* 2002 Mar;112(4):305-311.
8. Hansen TK, Thiel S, Wouters PJ, Christiansen JS, Van den Berghe G. Intensive insulin therapy exerts anti-inflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. *J. Clin. Endocrinol. Metab.* 2003 Mar;88(3):1082-1088.
9. Steinberg HO, Brechtel G, Johnson A, Fineberg N, Baron AD. Insulin-mediated skeletal muscle vasodilation is nitric oxide dependent. A novel action of insulin to increase nitric oxide release. *J. Clin. Invest.* 1994 Sep;94(3):1172-1179.
10. Dandona P, Aljada A, Bandyopadhyay A. The potential therapeutic role of insulin in acute myocardial infarction in patients admitted to intensive care and in those with unspecified hyperglycemia. *Diabetes Care.* 2003 Feb;26(2):516-519.
11. Malmberg K, Rydén L, Efendic S, Herlitz J, Nicol P, Waldenström A, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J. Am. Coll. Cardiol.* 1995 Jul;26(1):57-65.
12. Furnary AP, Gao G, Grunkemeier GL, Wu Y, Zerr KJ, Bookin SO, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J. Thorac. Cardiovasc. Surg.* 2003 May;125(5):1007-1021.
13. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive Insulin Therapy in Critically Ill Patients. *N Engl J Med.* 2001 Nov 8;345(19):1359-1367.
14. Weston C, Walker L, Birkhead J. Early impact of insulin treatment on mortality for hyperglycaemic patients without known diabetes who present with an acute coronary syndrome. *Heart.* 2007 Dec;93(12):1542-1546.
15. Anselmino M, Ohrvik J, Malmberg K, Standl E, Rydén L. Glucose lowering treatment in patients with coronary artery disease is prognostically important not only in established but also in newly detected diabetes mellitus: a report from the Euro Heart Survey on Diabetes and the Heart. *Eur. Heart J.* 2008 Jan;29(2):177-184.
16. Malmberg K, Rydén L, Wedel H, Birkeland K, Bootsma A, Dickstein K, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur. Heart J.* 2005 Apr;26(7):650-661.
17. Cheung NW, Wong VW, McLean M. The Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. *Diabetes Care.* 2006 Apr;29(4):765-770.
18. Sodi-Pallares, Bisteni A, Medrano GA, Testelli MR, De Micheli A. The polarizing treatment of acute myocardial infarction. Possibility of its use in other cardiovascular conditions. *Dis Chest.* 1963 Apr;43:424-432.
19. Sodi-Pallares D, Testelli MR, Fishleder BL, Bisteni A, Medrano GA, Friedland C, et al. Effects of an intravenous infusion of a potassium-glucose-insulin solution on the electrocardiographic signs of myocardial infarction. A preliminary clinical report. *Am. J. Cardiol.* 1962 Feb;9:166-181.
20. Clark RS, English M, McNeill GP, Newton RW. Effect of intravenous infusion of insulin in diabetics with acute myocardial infarction. *Br Med J (Clin Res Ed).* 1985 Aug 3;291(6491):303-305.
21. Gwilt DJ, Petri M, Lamb P, Nattrass M, Pentecost BL. Effect of intravenous insulin infusion on mortality among diabetic patients after myocardial infarction. *Br Heart J.* 1984 Jun;51(6):626-630.
22. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in the critically ill patients. *N. Engl. J. Med.* 2001 Nov 8;345(19):1359-1367.
23. Wiener RS, Wiener DC, Larson RJ. Benefits and Risks of Tight Glucose Control in Critically Ill Adults: A Meta-analysis. *JAMA.* 2008 Aug 27;300(8):933-944.
24. Kushner FG, Hand M, Smith SC, King SB, Anderson JL, Antman EM, et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update). A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation [Internet].* 2009 Nov 18 [cited 2009 Dec 1]; Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19923169>
25. Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur. Heart J.* 2008 Dec;29(23):2909-2945.

26. Meijering S, Corstjens A, Tulleken J, Meertens J, Zijlstra J, Ligtenberg J. Towards a feasible algorithm for tight glycaemic control in critically ill patients: a systematic review of the literature. *Critical Care*. 2006;10(1):R19.
27. Lipton JA, Barendse, Eenkhoorn, van der Ende, van Dam, van Ettinger, et al. Glucose control as a model for implementation of a clinical decision support system [Internet]. [cited 2009 Mar 11]; Available from: <http://www.cinc.org/Proceedings/2008/pdf/0661.pdf>
28. Vogelzang M, Loef BG, Regtien JG, van der Horst ICC, van Assen H, Zijlstra F, et al. Computer-assisted glucose control in critically ill patients. *Intensive Care Med*. 2008 Aug;34(8):1421-7.
29. Rood E, Bosman RJ, van der Spoel JI, Taylor P, Zandstra DF. Use of a Computerized Guideline for Glucose Regulation in the Intensive Care Unit Improved Both Guideline Adherence and Glucose Regulation. *J Am Med Inform Assoc*. 2005 Mar 1;12(2):172-180.
30. Wong X, Chase J, Shaw G, Hann C, Lotz T, Lin J, et al. Model predictive glycaemic regulation in critical illness using insulin and nutrition input: A pilot study. *Medical Engineering & Physics*. 2006 Sep;28(7):665-681.
31. Vriesendorp TM, DeVries JH, Holleman F, Dzoljic M, Hoekstra JBL. The use of two continuous glucose sensors during and after surgery. *Diabetes Technol. Ther*. 2005 Apr;7(2):315-322.
32. Fath-Ordoubadi F, Beatt KJ. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials. *Circulation*. 1997 Aug 19;96(4):1152-1156.
33. Krljanac G, Vasiljevic[combining acute accent] Z, Radovanovic[combining acute accent] M, Stankovic[combining acute accent] G, Milic[combining acute accent] N, Stefanovic[combining acute accent] B, et al. Effects of Glucose-Insulin-Potassium Infusion on ST-Elevation Myocardial Infarction in Patients Treated With Thrombolytic Therapy. *The American Journal of Cardiology*. 2005 Oct 15;96(8):1053-1058.
34. Mehta SR, Yusuf S, Díaz R, Zhu J, Pais P, Xavier D, et al. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. *JAMA*. 2005 Jan 26;293(4):437-446.
35. van der Horst ICC, Timmer JR, Ottervanger JP, Bilo HJG, Gans ROB, de Boer M, et al. Glucose-insulin-potassium and reperfusion in acute myocardial infarction: rationale and design of the Glucose-Insulin-Potassium Study-2 (GIPS-2). *Am. Heart J*. 2005 Apr;149(4):585-591.
36. Ceremużyński L, Budaj A, Czepiel A, Burzykowski T, Achremczyk P, Smielak-Korombel W, et al. Low-dose glucose-insulin-potassium is ineffective in acute myocardial infarction: results of a randomized multicenter Pol-GIK trial. *Cardiovasc Drugs Ther*. 1999 May;13(3):191-200.
37. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA*. 2006 Apr 5;295(13):1519-1530.
38. Yusuf S, Mehta SR, Díaz R, Paolasso E, Pais P, Xavier D, et al. Challenges in the conduct of large simple trials of important generic questions in resource-poor settings: The CREATE and ECLA trial program evaluating GIK (glucose, insulin and potassium) and low-molecular-weight heparin in acute myocardial infarction. *American Heart Journal*. 2004 Dec;148(6):1068-1078.
39. Early administration of intravenous magnesium to high-risk patients with acute myocardial infarction in the Magnesium in Coronaries (MAGIC) Trial: a randomised controlled trial. *Lancet*. 2002 Oct 19;360(9341):1189-1196.

Chapter 10

Hyperglycemia at admission and during hospital stay are independent risk factors for mortality in a high risk population admitted to the intensive cardiac care unit

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ABSTRACT

Aims: To assess the predictive value of admission- and average glucose levels in patients admitted to an intensive cardiac care unit (ICCU).

Methods and Results: Outcome was assessed in 1713 patients in whom glucose levels were measured during ICCU admission. Mean age was 63 ± 14 years, 72% (1227) were male, 17% (288) had known diabetes. Median (interquartile) glucose concentration at admission was 7.9 (6.5 – 10.1) mmol/L; median average glucose during hospitalization at the ICCU was 7.3 (6.7 – 8.3) mmol/L. Cox-regression analysis, including the variables age, gender, admission diagnosis, length of stay, prior (cardio)vascular disease and diabetes, revealed that a 1 mmol/l increase in admission glucose (above 9 mmol/l) was associated with a 10% (95% CI: 7% – 13%) increased risk for all cause mortality. In 893 patients with 3 or more measurements, a 1 mmol/l higher average glucose (above 8 mmol/l) was an additional independent predictor of mortality (HR 1.11, 95% CI: 1.03 – 1.20). At 30 days, 16.8% (97/579) of the patients with an admission glucose in the highest tertile (>9.8 mmol/L) had died vs. 5.2% (59 / 1134) of those with a lower admission glucose.

Conclusions: in a high risk ICCU population both a high admission glucose as well as a high average glucose during hospitalization at the ICCU were associated with an increased mortality, even when accounting for other risk factors and parameters of disease severity.

INTRODUCTION

Hyperglycemia in patients with acute medical conditions has been associated with increased mortality compared to normoglycemia in patients with the same condition (1). Indeed, outcome is improved with insulin treatment in hyperglycaemic patients presenting with acute myocardial infarction (2). However, the prognostic implications of initial (admission) and/or sustained hyperglycemia in high risk patients admitted to an Intensive Cardiac Care Unit (ICCU) have not been described. Therefore, the aim of this study was to evaluate the predictive value of both admission glucose- and average glucose levels in a high risk population of patients admitted to an ICCU with respect to all-cause mortality.

METHODS

Design and setting

The Thoraxcenter of the Erasmus University Medical Center is a tertiary care facility in Rotterdam, the Netherlands. The ICCU consists of 8 beds with a 1:1 - 1:2 nurse to patient ratio and 1400 - 1700 admissions per year. The present cohort study included patients admitted to the ICCU of the Thoraxcenter between 1 January 2007 and 28 July 2008. During that period 2396 patients were admitted to the ICCU. Glucose measurements were available in 1793 patients (75%) who were included in the analysis of the relation between admission glucose level and survival (figure 1).

In the 893 patients with 3 or more measurements, average glucose during admission was calculated using the area under the curve with linear interpolation (3).

During the study period, a simple sliding scale insulin protocol with a target glucose range of 4.5 - 7.0 mmol/L was used. The protocol has been described previously (4). Briefly, after each glucose measurement an advice was given with regard to dosage of insulin infusion, and when to repeat the glucose measurement. The advised interval between

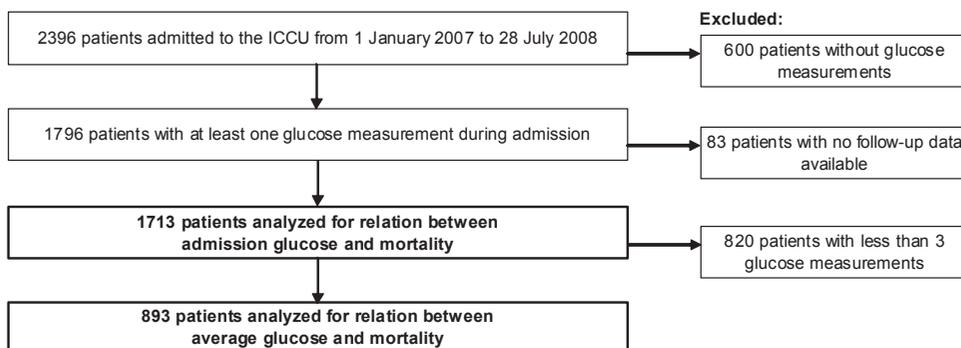


Figure 1: Patient inclusion

Acute measurements was shorter for high and low glucose values than for measurements in the target range. The protocol was nurse-driven, and initiated for all patients with an acute myocardial infarction or with a history of diabetes. For all other patients with elevated glucose levels a physician was consulted first. Copies of the protocol were available at the bedside of each patient and at the main ICCU desk. Plasma glucose concentration was measured in the hospital laboratory using the hexokinase method (Modular analytics EVO - P 800, Roche, Switzerland) in venous and arterial blood samples which were collected in F-EDTA tubes to stabilize glucose.

Data collection and follow-up

Patient demographics, admission diagnoses and medical history were registered in the patient data management system. Additional medical data was retrieved from hospital discharge letters and charts. Laboratory values (including glucose and troponin-T) were registered in the hospital information system. Follow-up data were obtained in 2010. The median (interquartile range) follow-up was 27 (23 – 34) months. All-cause mortality was determined from the hospital records and the municipal civil registries.

Statistics

Statistical analysis was performed with SPSS 15.0 (Chicago, USA). Continuous data were expressed as mean with standard deviation (SD) or median with interquartile range (IQR), as appropriate. Differences in continuous variables were evaluated using the Student T-test and analysis of variance. Differences in proportions were compared using the χ^2 test. Cox-regression analysis was used to determine the predictive value of admission and average glucose levels for all-cause mortality.

Admission glucose, average glucose, age, body mass index, duration of stay, troponin-T and APACHE-2 score were entered as continuous variables. Diabetes, hypertension, prior hypertension, prior renal disease and prior heart failure were entered as dichotomous variables. Dichotomous variables were also defined for combined prior atherothrombotic events (myocardial infarction or [transient] cerebrovascular event) and atherosclerotic disease (prior PCI or CABG, prior angina or peripheral atherosclerotic disease). Admission diagnosis was categorized into three groups: acute coronary syndrome (myocardial infarction or unstable angina), other severe cardiac disease (cardiac arrest, heart failure or arrhythmia), and others (including valvular heart disease and periprocedural care).

First, univariate analysis was performed. Subsequently, multivariate analysis was performed adjusting for age and gender, and for all variables that were associated ($P < 0.05$) with mortality in the univariate analysis. The risk was expressed as a hazard ratio (HR) with a corresponding 95% confidence interval (CI). A p-value < 0.05 was considered statistically significant.

RESULTS

During the study period data were collected in the 1793 patients (75% of all admissions) who had at least one glucose measurement. Follow-up data were available for 1713 patients (96%). Mean age was 63 ± 14 years, 72% (1227) were male and 17% (288) were known diabetics (table 1). A total of 1075 (70%) patients were admitted with an acute coronary syndrome. Median length of stay in the ICCU was 0.7 (0.2 – 1.5) days during which a median number of 3 (1 – 8) glucose measurements were done. 893 patients had 3 or more glucose measurements during their stay in the ICCU.

Table 1: Patient characteristics

	All patients (n = 1713)		Tertile of admission glucose				P-value
	value	n	highest (n = 579)		lower two (n = 134)		
Male gender	72%	1227	69%	398	73%	829	0.06
Age (years)	63.2 ± 14	1713	65.0 ± 13	579	62.2 ± 14	1134	<0.001
BMI (kg / m ²)	26.4 ± 4	899	26.9 ± 5	182	26.2 ± 4	606	0.03
History							
Diabetes	17%	288	31%	177	10%	111	<0.001
Hypertension	30%	519	33%	188	29%	331	0.2
Chronic pulmonary disease	8%	143	9%	49	8%	94	0.2
Renal disease	7%	123	6%	37	8%	86	0.03
Prior AMI	21%	366	24%	137	20%	229	0.3
Prior cerebrovascular event	9%	161	9%	54	9%	107	0.1
Prior angina	10%	175	7%	43	12%	132	<0.001
Prior PCI	17%	289	16%	92	17%	197	0.4
Prior CABG	9%	156	9%	54	9%	102	0.2
Periferal vascular disese	5%	80	5%	30	4%	50	0.7
Prior heart failure	8%	130	6%	33	9%	97	0.001
ICCU stay (days)	0.7 (0.2 - 1.5)	1713	0.8 (0.2 - 2.7)	579	1.6 (0.2 - 1.1)	1134	<0.001
APACHE-2 score	14 (10 - 21)	1222	16 (12 - 30)	440	13 (10 - 18)	782	<0.001
Suspected ACS	69.7%	1075	65.3%	358	72.1%	717	0.005
Final diagnosis							
Myocardial infarction	44%	761	52%	303	40%	458	
Unstable Angina	16%	267	8%	45	20%	222	
Angina, Stable	3%	47	2%	10	3%	37	
Cardiac arrest	6%	98	13%	73	2%	25	
Heart failure	7%	121	10%	60	5%	61	
Arrhythmia	7%	114	5%	29	8%	85	
Valvular disease	5%	80	2%	10	6%	70	
Procedure	5%	90	4%	21	6%	69	
Other	8%	135	5%	28	9%	107	
Glucose measurements (n)	3 (1 - 8)	1713	5 (1 - 15)	579	2 (1 - 6)	1134	<0.001
Admission glucose (mmol/l)	7.9 (6.5 - 10.1)	1713	11.7 (10.0 - 14.8)	579	6.9 (6.1 - 7.9)	1134	<0.001
Average glucose (mmol/l)	7.3 (6.7 - 8.3)	893	7.9 (7.2 - 9.3)	355	7.1 (6.5 - 7.4)	538	<0.001

Values are displayed as %, mean \pm Standard Deviation or median (25th - 75th percentile). BMI (Body Mass Index); AMI (Acute Myocardial Infarction); PCI (percutaneous coronary intervention); CABG (coronary artery bypass grafting); ICCU (Intensive Cardiac Care Unit); APACHE (Acute Physiology and Chronic Health Evaluation); ACS (Acute Coronary Syndrome). P value for comparison of highest vs. lower two tertiles.

Admission glucose level was 7.9 (6.5 – 10.1) mmol/l and, in patients with 3 or more measurements, average glucose level during admission was 7.3 (6.7 – 8.3) mmol/l. Patients with admission glucose in the highest tertile were older, more often had known diabetes and were less likely to have prior angina, heart failure or PCI. These patients also had a longer duration of admission and had a higher disease burden, as reflected by a higher APACHE-2 score, and higher severity of diagnoses such as acute myocardial infarction and heart failure.

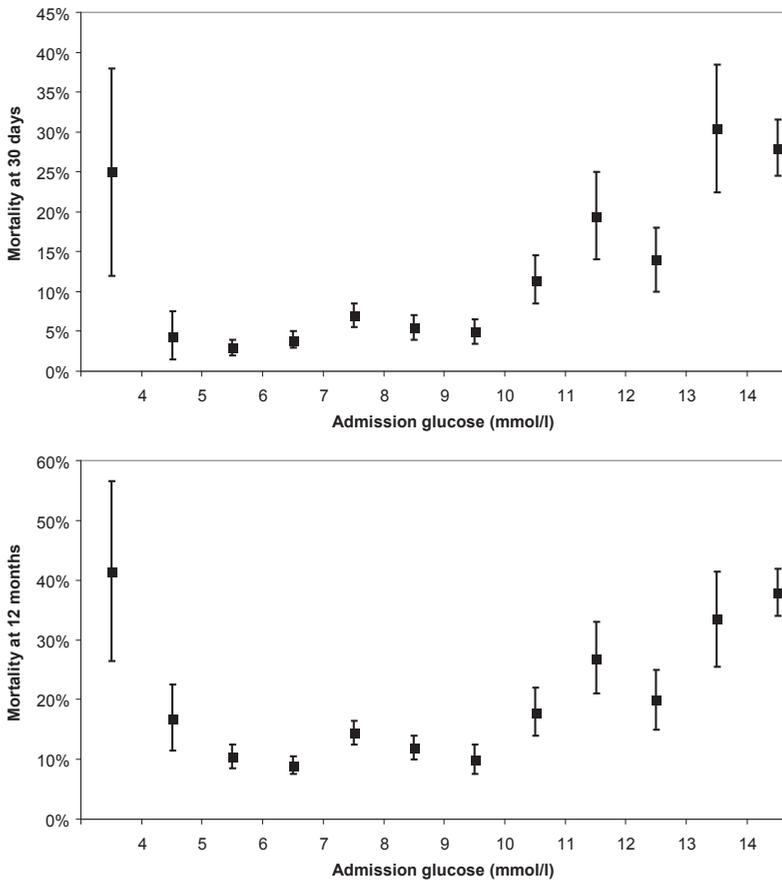
Mortality at 30 days was 9.1% (n = 156). At 12 months 272 patients (15.9%) had died, reflecting the high risk population admitted to the ICCU (table 2): in patients with acute myocardial infarction mortality was 7.3%. However, it should be appreciated that predominantly high risk patients were admitted to the ICCU, while patients at lower risk were either admitted to the medium care ward, or transferred to other hospitals. In the larger group of patients with myocardial infarction that were referred for primary percutaneous intervention in the Thoraxcenter, 30-day mortality was 3.8% during the same period.

Table 2: Mortality

	All patients		Tertile of admission glucose				P-value
	<i>value</i>	<i>n</i>	Highest <i>value</i>	<i>n</i>	Lower two <i>value</i>	<i>n</i>	
All patients (n = 1713)							
30-day mortality	9,1%	156	16,8%	97	5,2%	59	<0.001
12-month mortality	15,9%	272	23,7%	137	11,9%	135	<0.001
Patients with acute coronary syndrome (n = 1075)							
30-day mortality	5,6%	60	12,3%	44	2,2%	16	<0.001
12-month mortality	9,7%	104	16,6%	59	6,3%	45	<0.001

Mortality was relatively low in patients with normal or slightly elevated admission glucose levels but increased steeply in those with admission glucose levels higher than 9.0 mmol/l (figure 2), corresponding to the approximate cut-off for the upper tertile of admission glucose, which was 9.2 mmol/l. Indeed survival was similar for patients in the lower two tertiles for admission glucose as well as for average glucose, while mortality was significantly worse in the highest tertile (figure 3: P<0.001). Patients with admission glucose in the highest tertile were older, more often had known diabetes and were less likely to have prior angina, heart failure or PCI. These patients also had a longer duration of admission and had a higher disease burden, as reflected by a higher APACHE-2 score, and higher severity of diagnoses such as acute myocardial infarction and heart failure.

Hypoglycemia (< 4 mmol/l) on admission was observed in 12 patients (0.7%). We observed a high mortality in these patients of whom 3 had died at 30 days and 5 at 12 months. However, due to the limited numbers, this was not statistically significant.



Survival by Category of admission glucose

	< 4	4 - 5	5 - 6	6 - 7	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	> 14
30 day dead/alive	3 / 9	2 / 45	6 / 191	14 / 333	21 / 274	12 / 210	8 / 152	12 / 94	11 / 45	10 / 61	11 / 25	46 / 118
12 month dead/alive	5 / 7	8 / 39	21 / 176	31 / 316	42 / 252	27 / 195	16 / 144	19 / 86	15 / 41	14 / 56	12 / 24	62 / 102

Figure 2: Mortality at 30 days (top) and 1 year (bottom) by admission glucose. Patients with a glucose < 4 mmol/l and > 14 mmol/l were grouped into the lowest and highest categories respectively. Error bars represent standard error of the mean.

An increase of 1 mmol/l in admission glucose (above 9 mmol/l) was associated with a higher risk of death (HR 1.10, 95%CI 1.08 – 1.13) in univariate analysis (Table 3). This relationship remained statistically significant after adjustment for risk factors, admission diagnosis, APACHE-2 score and troponin-T levels, although the latter two were not available for all patients. Separate analyses were performed for the 1075 patients admitted with an acute coronary syndrome and for 333 patients with other severe cardiac disease, with similar results.

Table 3: Cox-regression analysis for relation between admission and average glucose and all cause mortality.

1 mmol/l increase in:	Univariate HR (95%CI)	Multivariate HR (95%CI)	Combined analysis* HR (95%CI)
Admission glucose	1.10 (1.08 – 1.13)	1.10 (1.07 - 1.13)	1.07 (1.04 - 1.10)
Average glucose	1.17 (1.10 – 1.23)	1.22 (1.14 - 1.30)	1.11 (1.03 - 1.20)

Variables used for multivariate analysis: age, gender, admission diagnosis (ACS, cardiacarrest/heartfailure/ arrhythmia, others), diabetes, prior renal disease, prior heart failure, prior thrombotic event (CVA/TIA/AMI), atherosclerotic disease (periferal, PCI/CABG, angina), duration of stay.

*Analysis including both the admission and average glucose into the regression model, thus the HR here represents the value of admission and average glucose independent of each other.

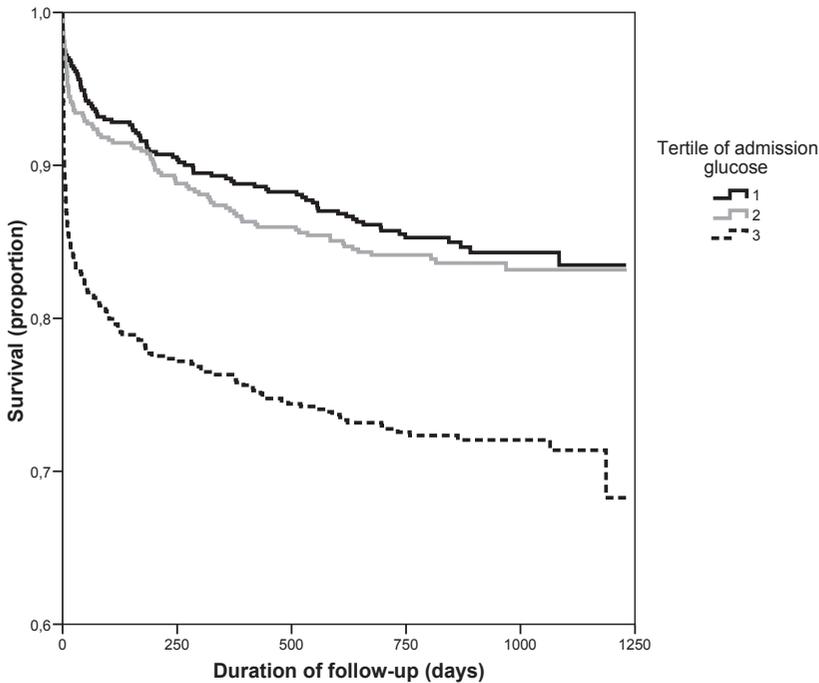


Figure 3: Survival curve by tertile of admission glucose. Tertile 1 (1.5 – 6.9 mmol/l); tertile 2 (7.0 – 9.1 mmol/l); tertile 3 (9.2 – 34.0 mmol/l).

For the 893 patients with 3 or more glucose measurements, the predictive value of the average glucose level, as an indicator of sustained hyperglycemia, was determined, using the same model as for admission glucose. Again a 1 mmol/l increase in average glucose above 8 mmol/l was associated with an increased risk of mortality (HR 1.17, 95%CI 1.10 – 1.13). In multivariate analysis, both the admission glucose level as well as the average glucose level were independently associated with mortality. Again, results were similar among patients with acute coronary syndromes and other cardiac disease.

DISCUSSION

In this high risk ICCU population both hyperglycemia at admission (glucose > 9 mmol/l) and sustained hyperglycemia as assessed by the average glucose level (> 8 mmol/l) were independent predictors of all-cause mortality. Furthermore, in patients with hypoglycemia (admission glucose < 4 mmol/l) we also observed a trend to an increased mortality, although the latter was not statistically significant due to the small number of patients with hypoglycaemia. Other studies reported similar relations between admission glucose levels and hospital mortality (5). We extend these findings to a high-risk population admitted to an Intensive Cardiac Care Unit and demonstrate for the first time that also sustained hyperglycaemia is an independent risk factor for mortality. Furthermore we demonstrate that this relation is not linear, since patients in the lower glucose tertiles had similar mortality rates, but that the increased risk starts at levels above 9 mmol/L for admission glucose and approximately 8 mmol/L for the average glucose level.

High admission glucose levels occur in patients with known and in those with so far unrecognised diabetes mellitus (6), but also may reflect the severity of other disease as a result of elevated catecholamine and cortisol levels. Additional conditions such as infection or sepsis may further disturb carbohydrate metabolism and glucose levels. These and several other factors are included in the APACHE-2 score (7). However, when this score was added to the regression model, this did not alter the findings of the current investigation, which confirms that the hyperglycemia per se is associated with impaired outcome (8-10). In patients with acute myocardial infarction, hyperglycemia is associated with higher free fatty acid concentrations (11), insulin resistance and impaired myocardial glucose metabolism, which may result in an increased oxygen consumption and consequently a more severe ischemic state and larger infarct size (12).

Our observations that both admission glucose > 9 mmol/l as well as sustained glucose levels over 8 mmol/l are independently associated with impaired outcome suggest that it would be appropriate to initiate insulin therapy in patients with glucose levels above 9 mmol/L, and aim for average glucose levels lower than 8 mmol/L. Additionally, the higher mortality in the patients with admission glucose < 4 mmol/l emphasize the need to prevent hypoglycaemia. In an intensive care setting, van den Berghe et al. (13) demonstrated a reduced mortality and morbidity during hospital admission among patients treated with glucose lowering insulin therapy. Similarly the DIGAMI study achieved better outcome with intensive insulin therapy (14). This benefit was, however, not confirmed in DIGAMI-2 (15), probably because of the low contrast in glucose levels among the different treatment regimens. Furthermore, in the more recent NICE sugar trial (16), an increase in hypoglycemic episodes and mortality was seen in the patients allocated to more intensive insulin therapy. Indeed, careful regulation of glucose levels in the ICCU is difficult to

Acute achieve (4,17), so targets should not be set tighter than necessary. Further studies are needed to investigate the optimal insulin treatment regimen to improve outcome in patients with acute cardiac disease.

The current study was performed in a high-risk patient population. It is important to note the high 30-day mortality rate for myocardial infarction: in the overall population of patients with acute myocardial infarction admitted to the ICCU (including those without glucose measurements) the 30-day mortality rate was 7.3%. However, this included patients in cardiogenic shock (9.2%) with a much higher mortality rate. The mortality rate for the patients admitted with acute myocardial infarction without cardiogenic shock was 3.8% during the study period, representative for a tertiary center. The Erasmus Medical Center treats approximately 650 patients per year with primary PCI. In addition to the uncomplicated patients with acute myocardial infarction, which are directly transferred after reperfusion treatment to surrounding hospitals, the center also treats the complex patients from other hospitals.

In this high-risk population, multivariate analysis demonstrated an independent and incremental prognostic value for admission and average glucose values. Similarly, in the DIGAMI study (14) of 620 diabetic patients with acute myocardial infarction, admission glucose was independently associated with mortality during 3.4 years follow-up. The admission glucose levels in DIGAMI (15.5 mmol/l) were higher than in the current study (7.9 mmol/l), as was the 30-day mortality rate (14% vs. 9.1%). Since most of our patients did not have diabetes, this reflects a greater disease severity of non-diabetic patients in the current study. Similar high mortality rates were reported in other studies of patients with acute coronary syndrome and high admission glucose and in elderly patients (>65 years) hospitalized for acute myocardial infarction (2,18).

Study limitations

Glucose values were not collected in all patients. Therefore patients without measurements were not included. These excluded patients represent the uncomplicated patients that were transferred back to the referring hospital or to a step-down unit.

Also, in sicker patients glucose levels may have been measured more often; thus hyperglycaemic episodes in less sick patients might have gone undetected resulting in an underestimation of average glucose in patients with less severe disease. However, the frequency of measurements was taken into account when calculating the average glucose level during admission.

CONCLUSION

Higher admission glucose and average glucose levels are associated with increased mortality in a high risk population of patients admitted to the ICU. Hyperglycemia is an independent risk factor of outcome, also after multivariate adjustment for other risk factors. Accordingly, a more aggressive glucose lowering treatment may improve outcome in these patients, provided that hypoglycaemia is avoided.

REFERENCES

1. Penfold S, Gouni R, Hamilton P, Richardson T, Kerr D. Immediate in-patient management of hyperglycaemia-confusion rather than consensus? *QJM*. 2008 Feb;101(2):87-90.
2. Weston C, Walker L, Birkhead J. Early impact of insulin treatment on mortality for hyperglycaemic patients without known diabetes who present with an acute coronary syndrome. *Heart*. 2007 Dec;93(12):1542-6.
3. Le Floch JP, Escuyer P, Baudin E, Baudon D, Perlemuter L. Blood glucose area under the curve. Methodological aspects. *Diabetes Care*. 1990 Feb;13(2):172-5.
4. Lipton JA, Barendse RJ, Akkerhuis KM, Schinkel AFL, Simoons ML. Evaluation of a clinical decision support system for glucose control: impact of protocol modifications on compliance and achievement of glycemic targets. In Press: *Critical Pathways in Cardiology*.
5. Asadollahi K, Beeching N, Gill G. Hyperglycaemia and mortality. *Journal of the Royal Society of Medicine*. 2007 11;100(11):503-507.
6. Rydén L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ, Cosentino F, Jönsson B, Laakso M, Malmberg K, Pori S, Ostergren J, Tuomilehto J, Thrainsdottir I, Vanhorebeek I, Stramba-Badiale M, Lindgren P, Qiao Q, Pori SG, Blanc JJ, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano JL, Deckers JW, Bertrand M, Charbonnel B, Erdmann E, Ferrannini E, Flyvbjerg A, Gohlke H, Juanatey JR, Graham I, Monteiro PF, Parhofer K, Pyörälä K, Raz I, Scherthaner G, Volpe M, Wood D. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur. Heart J*. 2007 Jan;28(1):88-136.
7. Junger A, Böttger S, Engel J, Benson M, Michel A, Röhrig R, Jost A, Hempelmann G. Automatic calculation of a modified APACHE II score using a patient data management system (PDMS). *Int J Med Inform*. 2002 Jun;65(2):145-57.
8. Norhammar A, Tenerz A, Nilsson G, Hamsten A, Efendic S, Rydén L, Malmberg K. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *The Lancet*. 2002 Jun 22;359(9324):2140-2144.
9. Beck JA, Meisinger C, Heier M, Kuch B, Hörmann A, Greschik C, Koenig W. Effect of Blood Glucose Concentrations on Admission in Non-Diabetic Versus Diabetic Patients With First Acute Myocardial Infarction on Short- and Long-Term Mortality (from the MONICA/KORA Augsburg Myocardial Infarction Registry). *The American Journal of Cardiology*. 2009 Dec 15;104(12):1607-1612.

10. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *The Lancet*. 2000 Mar 4;355(9206):773-778.
11. Tansey MJ, Opie LH. Relation between plasma free fatty acids and arrhythmias within the first twelve hours of acute myocardial infarction. *Lancet*. 1983 Aug 20;2(8347):419-422.
12. Oliver MF. Metabolic causes and prevention of ventricular fibrillation during acute coronary syndromes. *Am. J. Med.* 2002 Mar;112(4):305-311.
13. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. *N. Engl. J. Med.* 2001 Nov 8;345(19):1359-1367.
14. Malmberg K, Norhammar A, Wedel H, Rydén L. Glycometabolic state at admission: Important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction. Long-term results from the diabetes and insulin-glucose infusion in acute myocardial infarction (DIGAMI) study. *Circulation*. 1999;99(20):2626-2632.
15. Malmberg K, Rydén L, Wedel H, Birkeland K, Bootsma A, Dickstein K, Efendic S, Fisher M, Hamsten A, Herlitz J, Hildebrandt P, MacLeod K, Laakso M, Torp-Pedersen C, Waldenström A. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur. Heart J.* 2005 Apr;26(7):650-661.
16. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus Conventional Glucose Control in Critically Ill Patients. *N Engl J Med.* 2009 Mar 26;360(13):1283-1297.
17. Lipton JA, Barendse RJ, Schinkel AFL, Akkerhuis KM, Simoons ML, Sijbrands EJG. Effect of an alerting clinical decision support system for glucose control on protocol compliance and glycemic control in the intensive cardiac care unit. Submitted.
18. Kosiborod M, Rathore SS, Inzucchi SE, Masoudi FA, Wang Y, Havranek EP, Krumholz HM. Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. *Circulation*. 2005 Jun 14;111(23):3078-3086.

Chapter 11

Glucose control as a model for implementation of a clinical decision support system

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ABSTRACT

Glucose control in acute cardiac disease is difficult to achieve and may improve patient outcome. Because glucose levels were high at the Intensive Cardiac Care Unit, and adherence to a paper protocol was low, a web based decision support system for glucose control was developed. A board view of the currently admitted patients is provided; new glucose values are retrieved along with insulin infusion rates and patient data from the Patient Data Management System. For each new glucose value a pop-up is generated with the protocol advised action for insulin dosage and time for the next glucose measurement. Temporal trends in glucose and insulin values are displayed as an additional aid. An evaluation database is included in the design to provide feedback to the users on protocol compliance and glucose control. These data will also be used to improve the protocol.

INTRODUCTION

Glucose homeostasis in critical illness is altered due to changes in metabolism, release of hormones that counteract the normal action of insulin and an increase in hepatic glucose production; in addition the sensitivity of peripheral tissues to insulin may decrease (1). Hyperglycemia is also common in patients admitted with Acute Coronary Syndromes, and is associated with a more negative prognosis; possibly due to pro-inflammatory, pro-thrombotic and tissue damaging effects of glucose (2).

The importance of glucose control has led to a large number of studies and published protocols. Use of automated glucose protocols has been associated with increased protocol compliance and better achievement of glucose target levels (3).

Designing applications for clinical decision support, such as automating existing protocols, is a complex task, requiring continuous evaluation and refining of the system (4). The aim of this project was to develop a Clinical Decision Support System (CDSS) for glucose control at the Intensive Cardiac Care Unit (ICCU) that can be easily adapted for other CDSS applications.

BASELINE EVALUATION

An evaluation of the existing situation at the ICCU was done: glucose levels and protocol compliance were analyzed for all admissions. Data was used from ChartAssist (Dräger Medical, Andover MA, USA), the Patient Data Management System (PDMS) (5).

Glucose level and protocol compliance

From January 1, 2007 thru July 28, 2008, 2398 ICCU admissions were identified. Of these, 1788 had at least one glucose measurement during admission and were included into the analysis. In total 16221 glucose measurements were used (Table 1).

Glucose level during admission was calculated using the Area Under the Curve (6) and Hyperglycemic Index (7). For the majority (60,5%) of the admissions the average glucose level was above protocol target range (4,5 to 7,0 mmol/dl). Thirty-nine percent were within the range and 0,5% was below. Measurements were performed within the protocol advised time in 37% (a 10% margin was included). Insulin was dosed according to the protocol in 50%, lower in 46% and higher in 4% of the cases.

In short: the majority of the admissions had average glucose levels higher than the target range, and compliance with the protocol was low.

Workplace analysis

Nurse and physician workflow patterns were observed and interviews were conducted. The 8-bed ICCU uses a web-based PDMS (5) that includes demographic data, laboratory

Acute values and (IV) medications. The PDMS fully supports the nursing documentation; data from the PDMS are kept in a database which is replicated.

Laboratory measurements (including glucose) are performed using full blood samples (venous and arterial), which are determined at a nearby (approximately 25m) laboratory, where the sample is analyzed and the values are automatically entered into the Hospital Information System. There is an approximate delay of 20 minutes between sample acquisition and completed analysis; the nurse needs to check the PDMS regularly to see if the sample has been determined before taking action as advised by the paper protocol. The insulin infusion rate is adjusted, sometimes after consulting a physician, and the nurse manually enters the insulin dosage into the PDMS.

Table 1: Baseline glucose and protocol compliance

Population characteristics	
Mean age (years)	64 ± 14
Male gender	71%
Pre-existent Diabetes	20%
Number of glucose measurements	3 (1 - 43)
Length of ICCU admission (days)	0.7 (0 - 10)
Glucose values	
Average glucose during admission (mmol/l)	7.4 (5 - 12)
< 4.5 mmol/l	0.5%
4.5 - 7.0 mmol/l	39.0%
> 7.0 mmol/l	60.5%
Hyperglycemic index	0.71 (0 - 4.9)
Protocol compliance	
Glucose measurements on time	37%
Insulin dosage according to protocol	50%
Insulin dosage lower than protocol advice	46%
Insulin dosage higher than protocol advice	4%

Values are displayed as mean±SD or median (5 - 95 percentile)

Table 2: Excerpt from glucose protocol

Initial glucose value	Start Insulin Infusion at	remeasure
> 20 mmol/l	5 units/hour, notify physician	in 1 hour
17.1 - 20.0	4 units/hour	in 1 hour
14.1 - 17.0	3 units/hour	in 1 hour
11.1 - 14.0	2 units/hour	in 1 hour
7.1 - 11.0	1 units/hour	in 1 hour
< 7.0	no insulin	in 4 hours
Next glucose value	Insulin infusion	remeasure
> 11.0	ask physician about increase	in 2 hours
7.8 - 11.0	increase with 1 unit/hour	in 2 hours
7.1 - 7.8	increase with 0.5 unit/hour	in 2 hours
4.5 - 7.0	do not change	in 4 hours

The existing paper protocol (Table 2) is available at several locations on the ICCU, but not at bedside. It is a simple, rule-based protocol; rate of change in glucose value, nutritional status, medications, diurnal variation and history of diabetes are not taken into account.

Requirements for the glucose CDSS

Based on analysis of the current workflow, protocol limitations and technical possibilities, the following requirements were defined for the glucose CDSS:

- Notification of new glucose values with advice regarding insulin dosage and time of next measurement.
- Display of temporal trends in glucose values and insulin infusion rates.
- No manual data entry, straightforward and 'nurse-proof' interface.
- Use of PDMS data without compromising its speed, stability or manufacturer warranty.

DESIGN OF THE GLUCOSE CDSS

A board view display was developed (Figure 1), showing all eight ICCU beds. In each square colored bars represent glucose values; red indicating a value outside of target range, and green a value within. Insulin infusion rate is represented by a black line. Bars are displayed for measurements over the last 15 hours.

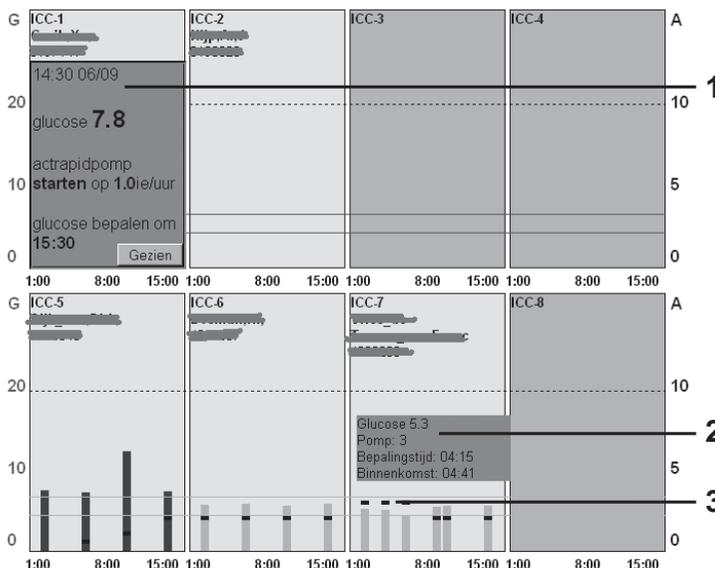


Figure 1: Eight ICCU beds are displayed; five admitted patients are shown, four with glucose values. The pop-up indicates a new value (1). Bars represent the preceding values; touching a bar will display the respective values (2). Insulin dosage is displayed by the black marks (3).

When a new glucose value is reported by the lab, a popup is displayed with the value and the protocol advised course of action: the adjustment in insulin infusion rate and the time when next glucose is to be determined. The popup can be closed with a finger press. Additionally the last popup can be recalled by touching the patient name. The glucose value and insulin infusion rate at a given time can be recalled by touching the respective bar. A 15-inch touch screen integrated PC was used, and mounted behind the nurses desk, easily accessible and clearly visible to all nurses.

Front-end design

The current design is a web 2.0 application, incorporating Simple Object Access Protocol, Asynchronous JavaScript and XML, and C#. The front end requests all available glucose values and insulin infusion rates of all (currently) admitted patients on the ICCU from the web service (see section on data acquisition and web service). The values are requested at a 10 second interval, followed by redrawing parts of the screen and generating pop-ups for new glucose values. This combination of web service and JavaScript allows for a quick screen redraw without using a 'hard page refresh'.

A web-based interface was chosen for the front-end design of the DSP screen. This was done for several reasons: it is lightweight, enables access to the screen from multiple locations, and enables a design that in future it can easily be switched from a 'nurse desk board view' to a 'single patient bedside' view.

Data acquisition and web service

The data required for the CDSS is stored at different locations on the different hospital based systems (figure 2). The glucose values are received from the Hospital Information System by a buffer and then sent to the PDMS. Replicated data from the commercial PDMS database is used; running the CDSS on the primary database could slow or lock the database, and would void the warranty. The glucose values and PDMS data are also stored in an evaluation database.

The CDSS is a web service consisting of three different components. First is a cache, which stores all glucose values, insulin infusion rates and patient information of the patients currently admitted to the ICCU. The cache is renewed every minute, reducing the strain on the PDMS database server for each request from the glucose screens. Second is a simple (based on the paper glucose protocol) rule engine which uses the insulin infusion rates and glucose levels obtained from the PDMS database and laboratory buffer respectively, to generate a patient specific advice, which is also stored in the cache. Last is a web service function which queries the cache and sends the data from the cache in XML to the requesting glucose screens.

IMPLEMENTATION AND EVALUATION

A team consisting of a research physician, cardiologist and nurse was formed to help with the development and testing of the application. On July 28 the project was presented and demonstrated to the nursing staff.

During a 4-week pilot starting on August 11, technical and user aspects of the application were evaluated at the end of each shift. Nurses were instructed to enter the reason for deviation from protocol as a note into the PDMS. These notes are, along with insulin infusion rates, glucose values, and touch-screen utilization, collected in an evaluation database (Figure 2). A query and calculations are done to determine protocol compliance, reasons for deviation and glucose control data. These data are evaluated with the team on a monthly basis and used to improve the application and protocol. Additional data, including disease and mortality information will be collected on a regular basis to investigate the relation between glucose control and patient outcomes.

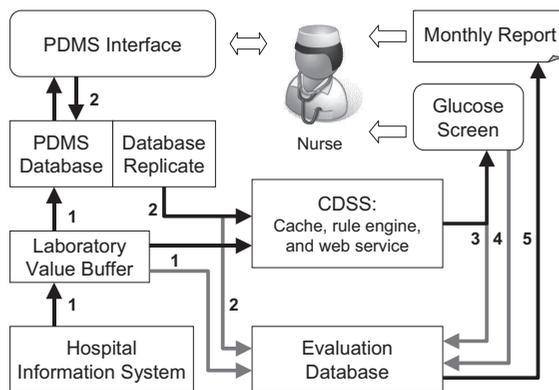


Figure 2: Overview of dataflow: 1. glucose values, 2. patient demographics and insulin infusion rates, reason for deviating from advice, 3. glucose protocol advice, 4. reaction times to advice, 5. feedback to users on use of system.

DISCUSSION

Analysis of existing ICU data showed that glucose control could be improved, and that compliance with the existing paper protocol was low.

Workflow evaluation revealed the following obstacles to protocol compliance: the absence of notification of new lab results, low availability of paper protocol and belief that adherence to protocol would lead to increased hypoglycaemic episodes.

A multidisciplinary approach using these findings as a starting point led to the current CDSS for glucose control.

Encountered challenges

As with any electronic system, the quality of the entered data determines the quality of the output: laboratory times are the times of blood sampling, as written on the lab form by the nurse, and may differ significantly from the actual time of blood sampling. Insulin dosage is also entered manually into the PDMS, thus incorrect entry may lead to incorrect perceived dosage by the CDSS and an incorrect advice.

Flaws in protocols or guidelines are more apparent in electronic than in paper form. Inadequate advice from a paper version can easily go unnoticed, whereas electronic versions are designed to actively confront the user. For this reason the users are asked to provide the reason for deviating from the protocol advice: this will help identify and resolve potential flaws in the protocol.

During the initial pilot the following additional reasons for deviating from the protocol were identified: method of feeding (normal, enteric tube or parenteral), specific medications (e.g. steroids), time of day and quickly declining glucose levels.

The next step of incorporating these factors into the CDSS without additional data entry may be challenging: some of these factors are not entered into the PDMS, and may not always require deviation from the protocol.

Lastly, the clinical problem remains a difficult and controversial one; glucose control in critically ill patients has many research questions, including the range in which levels should be kept, as well as which patients benefit most from a tight glucose control (8).

Future directions

The CDSS display is currently not available at the patient bedside; initial results from the pilot suggest that a display at a central location as well as the bedside would increase protocol compliance; the nurse would then be able to see the advice and at the same time adjust the insulin dosage accordingly. Ideally the CDSS would be integrated into the PDMS, thus eliminating the need for an extra patient bedside monitor.

CDSS in general, and the current system specifically, have enormous potential to collect data for protocol and guideline improvement. In the current setting data acquisition and validation is a time-consuming process. Use of a data warehouse where PDMS data is stored may facilitate the data retrieval in a form that is suitable for further analysis.

The current design is suited for many different types of protocols in the critical care environment; such as sedation, heparin, nutrition, ventilation, and others where the information needed is available in electronic format. The interface for multiple CDSS running at the same time will be challenging; assigning a level of importance to the CDSS notification may be useful to prevent 'alert fatigue'.

The current CDSS can be adapted to other units. With only minor adjustments it may be used on other intensive cares, as these have the highest level of electronic charting, but with additional changes it could also be used on the medium care wards.

CONCLUSION

A thorough investigation led to a system that fits into the workflow, requires no additional data input and prospectively collects data for evaluation.

Using a flexible web based platform a clinical decision support system for glucose control was developed.

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REFERENCES

1. Robinson LE, van Soeren MH. Insulin resistance and hyperglycemia in critical illness: role of insulin in glycemic control. *AACN Clin Issues*. 15(1):45-62.
2. Deedwania P, Kosiborod M, Barrett E, et al. **Hyperglycemia and Acute Coronary Syndrome: A Scientific Statement** From the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2008;117(12):1610-1619.
3. Rood E, Bosman RJ, van der Spoel JI, Taylor P, Zandstra DF. Use of a Computerized Guideline for Glucose Regulation in the Intensive Care Unit Improved Both Guideline Adherence and Glucose Regulation. *J Am Med Inform Assoc*. 2005;12(2):172-180.
4. Niland JC, Rouse L, Stahl DC. An Informatics Blueprint for Healthcare Quality Information Systems. *J Am Med Inform Assoc*. 2006;13(4):402-417.
5. Nelwan SP, van Dam TB, Meij SH, van der Putten NHJJ. Implementation and Use of a Patient Data Management System in the Intensive Care Unit: A Two-Year Experience. *CIC proceedings 2007*. 34:221-224.
6. Le Floch JP, Escuyer P, Baudin E, Baudon D, Perlemuter L. Blood glucose area under the curve. Methodological aspects. *Diabetes Care*. 1990;13(2):172-5.
7. Vogelzang M, van der Horst I, Nijsten M. Hyperglycaemic index as a tool to assess glucose control: a retrospective study. *Critical Care*. 2004;8(3):R122-R127.
8. Wiener RS, Wiener DC, Larson RJ. Benefits and Risks of Tight Glucose Control in Critically Ill Adults: A Meta-analysis. *JAMA*. 2008;300(8):933-944.

Chapter 12

Implementing a clinical decision support system for
glucose control for the intensive cardiac care

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ABSTRACT

Adherence to guidelines and protocols in clinical practice can be difficult to achieve. We describe the implementation of a Clinical Decision Support System (CDSS) for glucose control on the Intensive Cardiac Care Unit (ICCU) of the Erasmus MC. An existing paper protocol for glucose control was used for the CDSS rule set. In the first phase we implemented a proof of concept of a CDSS: a web 2.0 AJAX-driven web screen, which resulted in an improved adherence to the glucose guideline. This paper will reflect on the technical implementations and challenges of our experience with this process. The end product will allow: storage of guidelines in a shareable and uniform matter, presentation of guidelines in a more clear way to physicians, a more flexible platform to maintain guidelines, the ability to adjust guidelines to incorporate changes based on collected evidence from the CDSS and/or literature review, and be able to better review the outcome.

INTRODUCTION

The use and effects of CDSS systems in clinical practice have been studied extensively and have shown to be an effective mean to improve healthcare (1,2). At the Thoraxcenter of the Erasmus MC we have started to implement CDSS by automating the glucose protocol of the ICCU. Glucose regulation is difficult to achieve and may have significant implications for clinical outcome (3). Though the clinical problem is complex, the nature of the paper protocol was very straightforward and therefore a good starting point.

The ICCU of the Thoraxcentre treats cardiology patients who require intensive care. These patients have continuous monitoring of vital signs which are registered, along with other clinical data in a Patient Data Management System (PDMS), Innovian (4).

Paper Protocol

A simple, rule based, sliding scale glucose protocol was used and was available at each patient bedside. The protocol was nurse-driven and dependent on glucose measurements determined by the laboratory. Compliance was low regarding advised insulin dosage and timing of measurements: there was a lack of notification when new lab results were available and there was no reminder on when to re-determine glucose values. These factors were given as the main reasons for not adhering to the protocol.

The paper protocol uses the most recent glucose measurement to advise an action of starting, adjusting or stopping insulin pump, and advises to measure glucose again within a certain amount of time.

The lab results are sent to the patient monitor, the PDMS and the Electronic Patient Record (EPR). A retrospective study of the data in the PDMS system revealed low compliance the protocol (5).

The protocol rules could not be defined as a gold standard: users suggested that the protocol could be improved with regard to certain points.

METHODS

To achieve higher protocol compliance we decided to implant a CDSS that would resolve some of the previously mentioned problems. We deployed a medical touch screen computer at the nurse desk which displays the 8 beds of the ICCU with patient characteristics, previous glucose measurements and insulin pump settings (Figure 1). When a new glucose measurement for a patient arrives, a popup appears on the "bed" of the corresponding patient. The popup displays the glucose value, time of measurement, generated advice regarding insulin treatment and advised time for the next glucose measurement.

Figure 1 shows the Glucose Screen. This is a web 2.0 Ajax-driven web interface that polls the glucose web service every 10 seconds using SOAP. The web service component

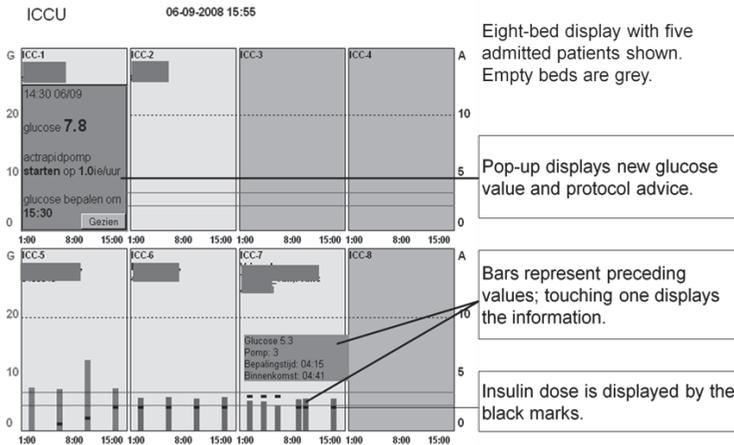


Figure 1: Screen shot of the Glucose Screen

runs on a web server and caches the lab values, the insulin pump settings and the generated decision of each lab value, every minute.

The database runs on SQL Server 2000 and is a real-time replicated database of the PDMS database. The database has extra tables for the glucose lab values, the generated advice and audit information. Figure 2 shows the dataflow of the application.

The guideline engine consists of an if-else structure, hard coded into the web service. The values needed for calculation of the generated advice are entered into the decision tree and a corresponding advice is returned.

We collected the data, the glucose value, the time of measurement, time of display and the time of reaction into this database.

RESULTS

In our setup the nurse no longer is required to actively look in the PDMS or EPR system to retrieve the latest measurement. The nurse can now easily discover new measurements and the generated advice by glancing at a fixed screen at the nursing station of the ward.

After implementation of the CDSS adherence to the glucose protocol increased when compared to baseline (5). During a 4 month period we collected 3418 glucose measurements. Retrospectively we analyzed 15360 glucose measurements from the same ICU from 18 months before the implementation of the CDSS. Patients that had less than 2 glucose measurements were not included in the analyses.

The percentage of glucose measurements performed on time (next measurement not later than the advised time + 10%) increased after implementation from 41% to 55%, an increase of 13.2% (95%CI 11.4% to 15.1% $P < 0.001$). Compliance with advised insulin dosage also improved from 48% to 58%, increase of 9.8% (95% CI 7.9% to 11.6% $P < 0.001$).

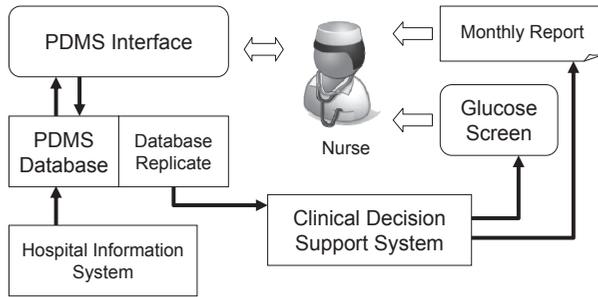


Figure 2: Dataflow chart for the Glucose Screen

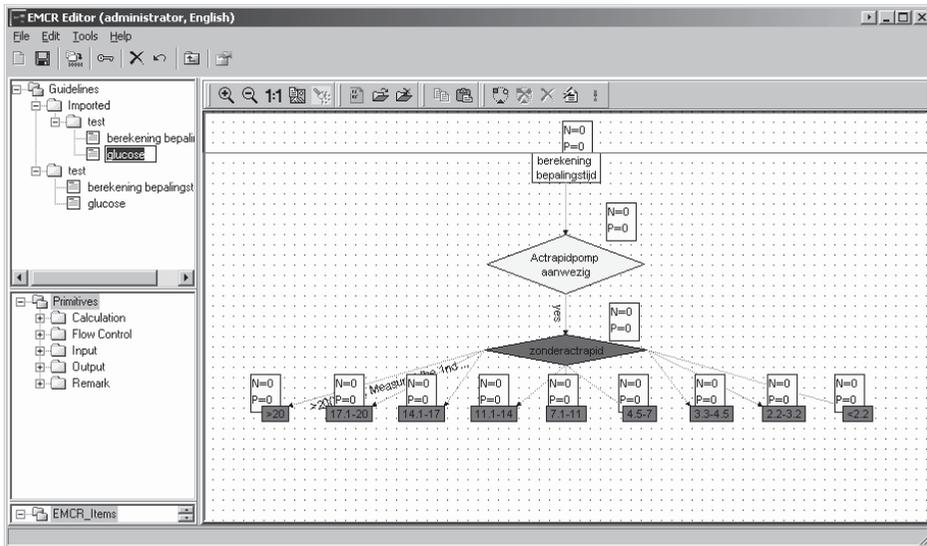


Figure 3: Screenshot of the KA-tool in Gaston displaying the Glucose decision tree

Future Work

One of the challenges in generating this application was retrieving the necessary data. Several sources, such as the hospital information system (HIS), the EPR built on the HIS and the PDMS provide the necessary data elements. The PDMS in itself receives data from the HIS (lab and patient demographics). Getting the necessary data from 3rd party applications can be challenging.

Currently we are extending the project with a third-party commercial decision support tool Gaston (6). The tool consists of a guideline executer and an interface to visually design guidelines. Also it has built-in support for data acquisition and several other features. Figure 3 shows the guideline editor. In this program physicians can specify the guidelines

themselves. These guidelines are immediately available from a web service when published. This gives us a clear distinction between guidelines and corresponding advice and the display of these guidelines on the screen.

With this extension we can focus our research more on implementation of CDSS and on how we can deliver the generated guidelines to the nurse or physician in the most efficient way possible. We want to extend the current application with this rule engine in our webservice. In a later phase we plan to implement a framework for transporting guidelines to other screens, applications and devices.

Many aspects of the implementation would be facilitated by an improved data integration of the different products and/or systems. A data warehouse solution would not work in the current setup, since the extraction would only be daily at most and not continuously. At the moment we are implementing HL7 to receive the lab data to be less dependent on the lab data in the PDMS.

The new improvements, Gaston and HL7 lab will facilitate and speed up the implementation of new guidelines in a faster and more flexible fashion.

DISCUSSION

We would like to expand CDSS into our organization. This will consist of working with 3-party software vendors that are capable of integrating CDSS into their application. Also we want to be able to extend CDSS to other platforms at the point of care e.g. PDA's.

Validating the outcome of our research is challenging as it is an iterative process with many different alterations: we have been upgrading software periodically on one side and also been improving the guideline on the other side. Each change has been documented and data has been collected until each point of the update. We chose to use different outcome measures for evaluating technical aspects, protocol compliance and clinical outcomes to be able to investigate the effect of each of these changes we made.

When interpreting the results it is important to consider that it is possible that changes to the guideline may result in increased adherence, but not always in improved clinical measures, and that technical improvements may lead to improved outcomes as well, irrespective of guideline adherence (e.g. a better graphical display of certain laboratory values may lead to earlier detection of abnormal values). Finally one must always be on the lookout for 'bugs' (both technical as inconsistencies in guidelines) that can adversely affect patient care.

REFERENCES

1. Garg, A.X., Adhikari, N.K.J., McDonald, H., et al.: Effects of Computerized Clinical Decision Support Systems on Practitioner Performance and Patient Outcomes: A Systematic Review. *JAMA* 293(10), 1223–1238 (2005)
2. Kaplan, B.: Evaluating informatics applications—clinical decision support systems literature review. *International Journal of Medical Informatics* 64(1), 15–37 (2001)
3. Weston, C., Walker, L., Birkhead, J.: National Audit of Myocardial Infarction Project NIFCOR. Early impact of insulin treatment on mortality for hyperglycaemic patients without known diabetes who present with an acute coronary syndrome. *Heart* 93(12), 1542–1546 (2007)
4. Nelwan, S., van Dam, T., Meij, S., van der Putten, N.: Implementation and use of a patient data management system in the intensive care unit: A two-year experience. *Computers in Cardiology* 2007, 221–224 (2007)
5. Lipton, J., Barendse, R., Eenkhoorn, E., et al.: Glucose Control as a Model for Implementation of a Clinical Decision Support System. In: *CIC Proceedings, Bolonga*, vol. 35, pp. 661–664 (2008)
6. de Clercq, P.A., Hasman, A., Blom, J.A., Korsten, H.H.M.: Design and implementation of a framework to support the development of clinical guidelines. *International Journal of Medical Informatics* 64(2-3), 285–318 (2001)

Chapter 13

Impact of an alerting clinical decision support system
for glucose control on protocol compliance and
glycemic control in the intensive cardiac care unit

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Submitted

ABSTRACT

Background: Glycemic control in patients with acute cardiac conditions is a clinical challenge but may substantially improve patient outcome. The aim of the current study was to evaluate the effect of implementing an automated version of the existing insulin protocol for glucose regulation in the Intensive Cardiac Care Unit (ICCU) on compliance with the protocol and achievement of glycemic targets.

Methods: During 11 months, data of 667 patients with two or more glucose measurements were evaluated, 425 before and 242 after implementation of the clinical decision support system (CDSS) for glucose control at the Erasmus Medical Center ICCU (Rotterdam, Netherlands).

Results: After implementation more patients had a mean glucose level within the target range of 81-126 mg/dl (31% vs. 43%; $P=0.01$); compliance with the advised measurement time increased from 40% to 52% ($P<0.001$) and compliance regarding insulin dosage increased from 49% to 61% ($P<0.001$). Monthly evaluation identified reasons for protocol non-compliance (eg. nutritional status and time of day) and will be used to improve the existing CDSS.

Conclusions: The CDSS implementation of an insulin protocol improved glucose regulation and protocol compliance in an Intensive Cardiac Care Unit, and identified targets for further improvement of the protocol.

The glucose values in this chapter are displayed as mg/dl: 18 mg/dl equals 1 mmol/L.

INTRODUCTION

Hyperglycemia in patients with acute cardiac conditions is associated with increased mortality compared to normoglycemic patients with the same condition (1). In hyperglycaemic patients presenting with acute myocardial infarction who received insulin therapy, lower mortality rates were observed (2). Protocols for regulation of glucose levels on high care and intensive care facilities are available in many hospitals. However, compliance to a glucose regulation protocol may be inadequate, especially when other treatments interfere with the timing of measurements and time to calculate new insulin infusion rates. The use of a computerized clinical decision support system (CDSS) for glucose regulation was shown to improve both protocol adherence and achievement of glycemic targets compared to a paper guideline in a mixed surgical / medical intensive care unit (3). Prior to the current study, glucose levels at our Intensive Cardiac Care Unit (ICCU) were inadequately controlled and adherence to the existing paper protocol was suboptimal. Therefore, a web based clinical decision support system (CDSS) for glucose control was developed (4,5).

The CDSS consists of a fully automated version of the existing paper protocol, developed to fit into the existing nursing workflow and requiring no manual data entry. A touch-screen monitor on the ICCU displays a board view of all currently admitted patients. New glucose values are automatically retrieved from the laboratory and displayed along with insulin infusion rates and patient data from the Patient Data Management System (PDMS). For each new glucose value, a pop-up is displayed with an advice for adaptation of the insulin infusion rate and timing of the next glucose measurement as appropriate. Temporal trends in glucose levels and insulin dosage are displayed as an additional aid.

The aim of the current study was to evaluate the impact of the CDSS on compliance with the existing protocol and on achievement of normoglycemia in the ICCU.

RESEARCH DESIGN AND METHODS

Study design

Data was collected for patients with two or more glucose measurements in the period prior to the implementation of the CDSS (1 January through 27 July 2008: group 1, 425 patients), as well as after (9 August through 30 November 2008: group 2, 242 patients). Data directly following implementation (28 July through 8 August 2008) was omitted from the analysis to allow for user familiarization with the CDSS.

The study was conducted at the ICCU of the Erasmus Medical Center in Rotterdam, the Netherlands. The unit consists of 8 beds with a 1:1 - 1:2 nurse to patient ratio and 1400 - 1700 admissions per year. Patients admitted included cardiac, non-surgical patients requiring intensive (cardiac) care. The nursing staff uses a web-based PDMS (ChartAssist, Draeger Medical, Andover, MA).

Insulin protocol characteristics and measurements

During the study period, a simple sliding scale protocol with a target glucose range of 81 - 126 mg/dl was used, which had been in use since 2006. An excerpt of the protocol is given in Figure 1. Copies of the protocol were available at the bedside of each patient and at the main ICCU desk. The protocol was nurse-driven, and initiated for all patients with an acute myocardial infarction or with a history of diabetes; for all other patients with elevated glucose levels a physician was consulted first. For each glucose value, the protocol provided an advice regarding insulin infusion rate and the time of the next measurement. After implementation of the CDSS, nurses were instructed to enter the reason for deviating from the protocol into the PDMS. Venous and arterial blood samples were collected in F-EDTA tubes to stabilize glucose. Plasma glucose was measured in the hospital laboratory using the hexokinase method (Modular analytics EVO - P 800, Roche, Switzerland).

Intervention

The design of the decision support system for glucose control is described in detail elsewhere (4,5). Briefly, using a touchscreen, a board view display was developed, showing all eight ICCU beds (Figure 2). Glucose values are represented for each bed by colored bars; bars are green when the value is within the target range, and red when too high or too low. The insulin infusion rate is represented by a black line. Bars are displayed for measurements over the last 15 hours. When a new glucose value is reported by the lab, a pop-up is displayed with the value and an algorithm-generated advice with respect to the adjustment in insulin infusion rate and the time for the next glucose measurement. This algorithm provides the same advice as the paper insulin protocol, allowing us to evaluate the effect of the CDSS interface rather than a combination of a new protocol and CDSS. The pop-up can be closed with a finger press. Additionally, the last pop-up can be recalled by touching the patient name. The glucose value and insulin infusion rate at a given time can be retrieved by touching the respective bar. The CDSS was designed as a web 2.0 application, incorporating Simple Object Access Protocol, Asynchronous JavaScript and XML, and C#. Patient data, glucose values and insulin infusion rates are requested at a 10-second interval and provided by a real-time replicated database of the PDMS. A 15-inch touchscreen integrated PC was used for the interface, and mounted behind the nurse's desk, easily accessible and clearly visible to all nurses.

Data collection

Patient demographics, admission diagnoses and medical history were registered in the PDMS. Glucose values were registered in the hospital information system. Insulin infusion rates and reasons for not complying with the protocol were also retrieved from the PDMS. For each patient, the following values were computed: mean glucose value (using the area under the curve methodology with linear interpolation (6)), hyperglycaemic index (7)

Initial glucose value	Start Insulin Infusion at	remeasure
>360 mg/dl	5 units/hour, notify physician	in 1 hour
308 - 360	4 units/hour	in 1 hour
254 - 307	3 units/hour	in 1 hour
200 - 253	2 units/hour	in 1 hour
128 - 199	1 units/hour	in 1 hour
< 128	no insulin	in 4 hours

Next glucose value	Insulin infusion	remeasure
> 198	ask physician about increase	in 2 hours
140 - 198	increase with 1 unit/hour	in 2 hours
128 - 139	increase with 0,5 unit/hour	in 2 hours
81 - 127	do not change	in 4 hours

In case of hypoglycemia	Insulin infusion	remeasure
59 - 80	decrease infusion rate by 50%	in 1 hour
40 - 58	stop insulin infusion, ensure sufficient glucose intake	in 1 hour
< 40	stop insulin infusion, administer 10g glucose intravenously	< 1 hour

Figure 1: Insulin protocol as used during study period. The protocol was available at patient bedside and nurse’s desk. Insulin (solution 50 units Actrapid™ / 50 ml glucose 5%) was dosed intravenously using an infusion pump. [18 mg/dl = 1 mmol/l]

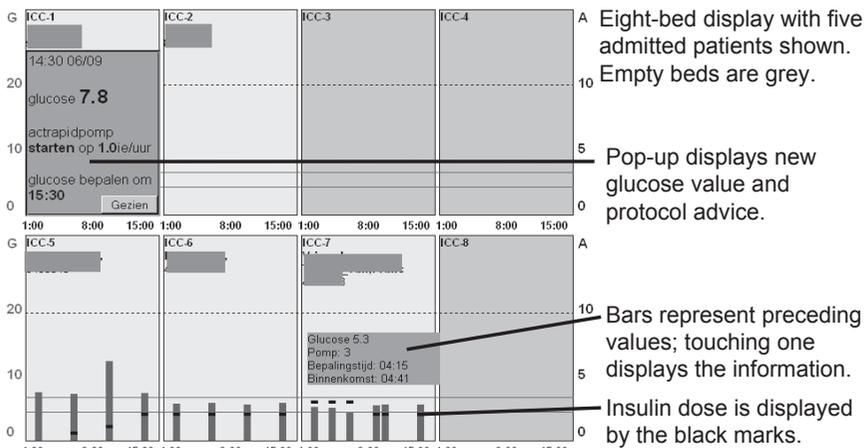


Figure 2: An image of the glucose Clinical Decision Support System, as displayed on a touchscreen. Eight Intensive Cardiac Care Unit (ICC) beds are displayed; five admitted patients are shown, four with glucose values. Beds 3, 4 and 8 are empty. The pop-up in the first bed indicates a new value. Bars as displayed in beds 5 - 7 represent the preceding values; touching a bar will display the respective value. Insulin dosage is displayed by the black marks.

and the percentage of admission time that glucose values were above the upper target level (126mg/dl). Hypoglycemic episodes were quantified and defined as any value lower than 58 mg/dl. Protocol compliance with respect to the timeliness of measurement was determined as the proportion of measurements done within the advised time from the previous measurement, with a 10% outer margin. Protocol compliance with respect to insulin dosage was determined using the insulin infusion setting between the glucose

Acute measurement generating the advice and the subsequent measurement. Evaluation of timeliness was done for all measurements except for the first; evaluation of correct insulin dosage was done for all measurements except for the last. Reasons for non-compliance were collected and stored in a database. First, nurses were instructed to enter the reason for deviation from the protocol into the PDMS, they could also choose to write down comments in a notebook present next to the touch-screen. Lastly, a study investigator (JL) was available on weekdays and by phone over weekends and night to answer questions and receive feedback.

Statistical analysis

Statistical analysis was done with SPSS 15.0 (Chicago, USA). Continuous data were expressed as mean with Standard Deviation (SD) or median values with interquartile range (IQR) as appropriate. Student's t-test and analysis of variance were used to analyze continuous data between the groups. Differences between proportions were compared using the χ^2 test. $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics and glucose levels

A total of 667 patients were included; 425 in group 1 and 242 in group 2. Baseline characteristics are displayed in Table 1 and were similar in the two groups. Mean age was 63 ± 14 years; 70% were male. Median length of stay was 1.0 (0.7 – 2.5) days during which 6 (3 - 15) glucose measurements were done. In total 10,433 glucose measurements were analyzed.

The mean glucose levels of the patients are displayed in Figure 3. An increase in the percentage of patients with an average glucose level within the target range of 81-126 mg/dl was seen of 12% (95% Confidence Interval [CI] 4 – 19%; $P = 0.003$). However, even after implementation, 57% of the patients still had a mean glucose level above the upper limit. Moreover, during admission to the ICCU, patients were hyperglycaemic (>126 mg/dl mmol/l) 40% (IQR 16 - 75%) of the time. This was 44% (IQR 17 - 78%) in group 1 versus 35% (IQR 13 - 74%) in group 2. However, this difference did not reach statistical significance ($P = 0.8$). The incidence of hypoglycaemia was low (1,2% of the measurements were <58 mg/dl) and did not differ between the two groups.

Protocol compliance and reasons for deviation

Compliance to the insulin protocol is displayed in Table 2 and was, higher in group 2. However still 48% of the measurements were delayed (i.e. done $>10\%$ later than the protocol recommended). Compliance with the recommended insulin dosage was higher in group 2 as well; however, insulin was still underdosed in 33% of the cases after implementation.

Table 1: Patient characteristics.

	Group 1	Group 2	All
Patients (n)	425	242	667
Age (years)	63.1 ± 14	63.2 ± 14	63.1 ± 14
Male gender (%)	68.7%	71.1%	69.6%
History of Diabetes (%)	20%	17%	19%
Body mass index (kg/m ²)	26.8 ± 5	26.6 ± 4	26.7 ± 4
Duration stay (days)	1.05 (0.7 - 2.5)	1.00 (0.6 - 2.6)	1.03 (0.7 - 2.5)
Measurements (n)	6 (3 - 14)	6 (3 - 16)	6 (3 - 15)
Incidence of hypoglycemia (<58mg/dl)	1.2%	1.2%	1.2%

Variables are displayed as mean ± Standard Deviation or median (Inter Quartile Range) as appropriate. Differences in parameters between group 1 and 2 were not statistically significant. [18 mg/dl = 1 mmol/l]

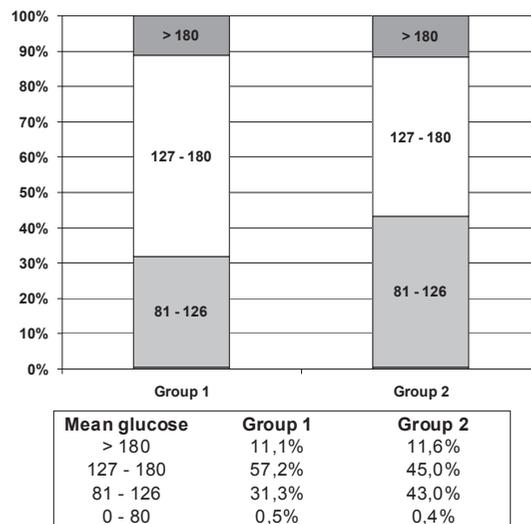


Figure 3: Mean glucose levels during admission before (group 1) and after (group 2) implementation of the computerized decision support system for glucose control. Patients are grouped according to the mean glucose level during admission. [18 mg/dl = 1 mmol/l]

Table 2: Protocol compliance

	Group 1	Group 2	All
Time measurement			
on time (+10%)	39,5%	51,8%	44,3%
delayed	60,5%	48,2%	55,7%
Insulin dosage			
too low	46,0%	32,9%	45,4%
as recommended	48,9%	60,6%	59,9%
too high	5,1%	6,4%	6,1%

Protocol compliance was determined for each glucose measurement and is described in "data collection" of the Research Design and Methods section.

Nurse-reported reasons for deviating from the protocol advice are displayed in Table 3. Nutrition-related reasons were most frequently reported. This included a reduction in insulin dosage given when the continuous feeding was interrupted or reduced. In the case of decreasing glucose levels, lower insulin dosage was administered than prescribed; the protocol did not take trends into account. Physician's order included giving an extra bolus of insulin, but also refraining from starting insulin treatment in mild hyperglycaemia. Dosage was reduced at night in some patients that tended to have lower glucose levels during the previous nights. Other reasons included less frequent glucose measurements in patients with stable, non-elevated glucose levels, patients with highly variable glucose levels and patients leaving the ward to undergo a procedure.

Table 3: Reasons for protocol deviation

Reason	Frequency
Nutrition related	22,9%
Decreasing glucose	15,2%
Physician's order	11,3%
Nighttime	9,1%
Insulin bolus needed	6,9%
Other	34,6%

(n = 109)

DISCUSSION

We hypothesized that introducing an electronic version of the existing paper protocol would lead to an improvement in compliance with the protocol, and improved glucose regulation. The implementation of the CDSS for glucose regulation led to an increased protocol compliance with regard to the timing of glucose measurements and with regard to the dosage of insulin. Also, this increased protocol compliance was associated with an improved glycemic control with significantly more patients having mean glucose levels within the target range. However, even after implementation, the mean glucose levels were still above the target range in the majority of the patients and deviation from the protocol advice still occurred frequently, illustrating the difficulty of glucose regulation in the ICCU setting.

The CDSS interface used at our ICCU was well received by the nurses: the visibility was good and improved the awareness to the new glucose values. Our findings with regard to the effect of a computerized vs. paper protocol are in line with other studies. Previous studies however typically report the combined effect of an automated interface with a new algorithm, and only include patients admitted for a prolonged period. Also, most studies take place in a general ICU setting with a more homogenous patient population.

We described the effect of a CDSS interface applied to an existing insulin protocol on compliance and glucose levels when implemented for all eligible patients admitted to an ICCU.

Computerized insulin protocols

Strict glycemic control is a controversial issue in critical care: many different glucose protocols exist for the intensive care setting and have been reviewed extensively (8,9) and the effect of automating insulin treatment advice has been investigated, but in contrast to the current study, most use a different insulin protocol in the electronic version than the paper protocol.

Rood et al. (3) and Boord et al. (10) described that the duration of time that a patient's glucose levels were within the protocol advised range increased 10% (54% with CDSS vs. 44% in the paper protocol group). Thomas et al. (11) described a decrease of mean glucose levels after implementation of an insulin dosage calculator from 119 ± 29 to 112 ± 23 mg/dl, whereas mortality remained the same. Morris et al. (12) described the implementation of an electronic algorithm in four different hospitals. They found a slightly lower mean glucose level (115 vs. 116 mg/dl) and a higher percentage of measurements within the target range (42% vs. 39%) compared to the use of a paper protocol. Additionally, they reported a high (98%) acceptance of recommendations by bedside clinicians.

In a multicentered randomized controlled trial, Plank et al. (13) included 60 patients and randomized to a fully automated algorithm or routine glucose protocols. They reported an increased time within the target glycemic range with the automated algorithm, however it required a glucose sampling every 60 minutes. The effect is likely to be a combination of an improved algorithm (with frequent glucose sampling), and an automated interface.

Amrein et al.(14) described an enhanced model predictive control algorithm in 20 patients admitted to the intensive care unit, with a graphical user interface and achieved tight glycemic control in 58% of the time the algorithm was applied. This protocol also required frequent measurements (the mean interval was 1,7 hours) and the study included patients that were expected to be admitted for at least 5 days.

Vogelzang et al.(15) introduced a computer program for glucose regulation, GRIP (Glucose Regulation for Intensive care Patients): glycemic target range (72 - 135 mg/dl) was achieved in 78% of the patients admitted to a surgical intensive care unit. However, they did not compare the computerized algorithm with a paper protocol.

The current study demonstrates that the CDSS improves adherence to the protocol as well as glycemic control in patients admitted to the ICCU, and that the method of implementation provided easy insight into reasons for non-compliance that can be used to improve the algorithm.

Reasons for deviation from the insulin protocol

In the current study, deviation from the protocol advice occurred in more than a third of the instances, even after implementation of the CDSS. We were however easily able to collect information on non-compliance. The main reason for deviation from the protocol was to prevent hypoglycaemia when glucose levels were decreasing. The protocol used was limited in its ability to include trends in glucose values; the graphic interface provided trend information, and may explain the consistent low incidence of hypoglycaemia, even after implementation of the CDSS. Variations in caloric intake were the next main reason for deviating from the recommended dosage. Patients in the ICCU differ greatly in their caloric intake; some receive continuous feeding by gastric or intravenous access, others take normal meals. Other reasons included need for extra insulin boluses in extreme hyperglycemia, not being able to measure within the advised time period due to diagnostic or therapeutic procedures, and unstable patients with highly variable glucose levels.

Future directions

The CDSS was used to implement further iterations of the protocol. The first modification was introduced on 1 December 2008 to take into account trends in glucose values and included an instruction to measure glucose one hour after a change in enteral feeding. In December 2009 further modifications were made, including a protocol for managing insulin therapy for patients around mealtimes (16). Further improvements to the CDSS interface are planned and include displaying the values at the patient bedside in addition to the nurse's desk, and a notification when the next glucose measurement is due.

Glucose measurements were taken from venous and arterial blood samples, and sent to the laboratory for analysis. This resulted in a delay of 5 to 25 minutes between time of sampling and the result. The laboratory determination is more accurate than point-of-care systems, but this advantage may be lost due to the delay and the point-of-care measurement may therefore be more appropriate. Ultimately a closed loop system using a continuous glucose sensor coupled to an algorithm driven insulin pump might provide optimal glycemic regulation. However, even though the accuracy of glucose sensor devices is high, also in the intensive care setting (17,18), a risk for undetected hypoglycaemia remains (19), especially in the presence of impaired skin perfusion.

Optimal glycemic targets for ICCU patients remain unclear. The initial studies by Malmberg et al. (20) and Van den Berghe et al. (22) showed a survival advantage for tight glycemic control (72 – 108 mg/dl). However, later studies by Malmberg et al. (23) and the NICE-SUGAR investigators (25) found increased incidence of hypoglycaemia, and in the case of the NICE-SUGAR trial, an increased mortality in the tightly regulated group. The current ACC/AHA guidelines for management of acute myocardial infarction (26) advise a threshold of 180 mg/dl for initiating glucose lowering therapy. Further work is needed to determine optimal glucose targets for the intensive cardiac care setting.

CONCLUSIONS

Use of a CDSS to implement a paper insulin protocol in the ICCU resulted in an absolute 12% increase in protocol compliance with regard to timing of glucose measurements and advised insulin dosage. After installation of the CDSS, the percentage of patients with a mean glucose level within target range also increased with 12%, however 57% remained above the target range.

Reasons for non-compliance were inventoried and will be used to improve the protocol with regard to temporal trends and caloric intake. Further work is needed to validate and establish optimal target ranges and improved measurement techniques for the ICCU setting.

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REFERENCES

1. Penfold S, Gouni R, Hamilton P, Richardson T, Kerr D. Immediate in-patient management of hyperglycaemia-confusion rather than consensus? *QJM*. 2008 Feb;101(2):87-90.
2. Weston C, Walker L, Birkhead J. Early impact of insulin treatment on mortality for hyperglycaemic patients without known diabetes who present with an acute coronary syndrome. *Heart*. 2007 Dec;93(12):1542-6.
3. Rood E, Bosman RJ, van der Spoel JI, Taylor P, Zandstra DF. Use of a Computerized Guideline for Glucose Regulation in the Intensive Care Unit Improved Both Guideline Adherence and Glucose Regulation. *J Am Med Inform Assoc*. 2005 Mar 1;12(2):172-180.
4. Barendse R, Lipton J, van Ettinger M, Nelwan S, van der Putten N. Implementing a Clinical Decision Support System for Glucose Control for the Intensive Cardiac Care [Internet]. In: *Artificial Intelligence in Medicine*. 2009 [cited 2009 Sep 30]. p. 161-165. Available from: http://dx.doi.org/10.1007/978-3-642-02976-9_21
5. Jonathan A. Lipton, Rogier Barendse, Stefan Nelwan, Dam TV, Maarten van Ettinger, Niek van der Putten. Protocol Adherence on the Cardiac Intensive Care Unit: Glucose Control as a Model for Implementation of Clinical Decision Support [Internet]. In: *CINC 2008*. Bologna: 2008 [cited 2009 Mar 2]. Available from: <http://www.cinc.org/Proceedings/2008/pdf/0661.pdf>
6. Le Floch JP, Escuyer P, Baudin E, Baudon D, Perlemuter L. Blood glucose area under the curve. Methodological aspects. *Diabetes Care*. 1990 Feb;13(2):172-5.
7. Vogelzang M, van der Horst I, Nijsten M. Hyperglycaemic index as a tool to assess glucose control: a retrospective study. *Critical Care*. 2004;8(3):R122-R127.
8. Van Herpe T, De Moor B, Van den Berghe G. Towards closed-loop glycaemic control. *Best Pract Res Clin Anaesthesiol*. 2009 Mar;23(1):69-80.
9. Meijering S, Corstjens A, Tulleken J, Meertens J, Zijlstra J, Ligtenberg J. Towards a feasible algorithm for tight glycaemic control in critically ill patients: a systematic review of the literature. *Critical Care*. 2006;10(1):R19.
10. Boord JB, Sharifi M, Greevy RA, Griffin MR, Lee VK, Webb TA, et al. Computer-based Insulin Infusion Protocol Improves Glycemia Control over Manual Protocol. *J Am Med Inform Assoc*. 2007 May 1;14(3):278-287.
11. Thomas AN, Marchant AE, Ogden MC, Collin S. Implementation of a tight glycaemic control protocol using a web-based insulin dose calculator. *Anaesthesia*. 2005 Nov;60(11):1093-100.
12. Morris AH, Orme J, Truwit JD, Steingrub J, Grissom C, Lee KH, et al. A replicable method for blood glucose control in critically ill patients. *Crit Care Med*. 2008;36(6):1787-95.

13. Plank J, Blaha J, Cordingley J, Wilinska ME, Chassin LJ, Morgan C, et al. Multicentric, randomized, controlled trial to evaluate blood glucose control by the model predictive control algorithm versus routine glucose management protocols in intensive care unit patients. *Diabetes Care*. 2006 Feb;29(2):271-6.
14. Amrein K, Ellmerer M, Hovorka R, Kachel N, Parcz D, Korsatko S, et al. Hospital glucose control: safe and reliable glycemetic control using enhanced model predictive control algorithm in medical intensive care unit patients. *Diabetes Technol. Ther*. 2010 May;12(5):405-412.
15. Vogelzang M, Zijlstra F, Nijsten MW. Design and implementation of GRIP: a computerized glucose control system at a surgical intensive care unit. *BMC Med Inform Decis Mak*. 2005;5:38.
16. Lipton JA, Barendse RJ, Akkerhuis KM, Schinkel AFL, Simoons ML. Evaluation of a clinical decision support system for glucose control: impact of protocol modifications on compliance and achievement of glycemetic targets. Submitted.
17. Logtenberg SJ, Kleefstra N, Snellen FT, Groenier KH, Slingerland RJ, Nierich AP, et al. Pre- and postoperative accuracy and safety of a real-time continuous glucose monitoring system in cardiac surgical patients: a randomized pilot study. *Diabetes Technol. Ther*. 2009 Jan;11(1):31-37.
18. Holzinger U, Warszawska J, Kitzberger R, Herkner H, Metnitz PGH, Madl C. Impact of shock requiring norepinephrine on the accuracy and reliability of subcutaneous continuous glucose monitoring. *Intensive Care Med*. 2009 Aug;35(8):1383-1389.
19. Rabiee A, Andreasik RNV, Abu-Hamdah R, Galiatsatos BSP, Khouri Z, Gibson BR, et al. Numerical and clinical accuracy of a continuous glucose monitoring system during intravenous insulin therapy in the surgical and burn intensive care units. *J Diabetes Sci Technol*. 2009;3(4):951-959.
20. Malmberg K, Rydén L, Efendic S, Herlitz J, Nicol P, Waldenström A, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J. Am. Coll. Cardiol*. 1995 Jul;26(1):57-65.
21. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in the critically ill patients. *N. Engl. J. Med*. 2001 Nov 8;345(19):1359-1367.
22. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive Insulin Therapy in Critically Ill Patients. *N Engl J Med*. 2001 Nov 8;345(19):1359-1367.
23. Malmberg K, Rydén L, Wedel H, Birkeland K, Bootsma A, Dickstein K, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur. Heart J*. 2005 Apr;26(7):650-661.
24. Malmberg K, Rydén L, Wedel H, Birkeland K, Bootsma A, Dickstein K, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur. Heart J*. 2005 Apr;26(7):650-661.
25. The NICE-SUGAR Study Investigators. Intensive versus Conventional Glucose Control in Critically Ill Patients. *N Engl J Med*. 2009 Mar 26;360(13):1283-1297.
26. Kushner FG, Hand M, Smith SC, King SB, Anderson JL, Antman EM, et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update). A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* [Internet]. 2009 Nov 18 [cited 2009 Dec 1]; Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19923169>

Chapter 14

Evaluation of a clinical decision support system for glucose control: impact of protocol modifications on compliance and achievement of glycemic targets

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ABSTRACT

Treating hyperglycemia may improve patient outcome, but is a clinical challenge. Three variations of a computerized insulin protocol were compared with regard to protocol compliance and achievement of glucose target levels. In group 1 the existing protocol was applied, in group 2 the protocol was modified to account for decreasing glucose values; group 3 had a higher threshold for initiating insulin, wider glucose target ranges, and included instructions to regulate glucose around mealtimes.

From 28 July 2008 until 1 February 2010 data from 1255 patients admitted to our Intensive Cardiac Care Unit (ICCU) with at least two glucose measurements were analyzed. Mean age was 64 ± 15 years, 66% were male, 21% had diabetes. Groups 1 to 3 included 269, 814 and 142 patients respectively.

Protocol compliance in group 2 was lower with 44% of the glucose measurements performed on time vs. 51% in group 1 ($P < 0.001$) and insulin was dosed correctly in 57% vs. 67% ($P < 0.001$). In group 3, compliance increased: 52% of the measurements were done on time, and insulin was dosed correctly in 71%. Average glucose levels increased in group 3 due to a higher threshold for starting insulin and a wider target range: 70% (group 1), 66% (group 2) and 61% (group 3) had an average glucose of < 8 mmol/l ($P < 0.001$). Also, we observed a decreasing trend in incidence of hypoglycemia and reporting of non-compliance. Further Improvements in glucose measurement technology and protocols are needed to optimally treat hyperglycemia in the ICCU.

INTRODUCTION

Hyperglycemia in patients with acute cardiac conditions is associated with increased mortality compared to normoglycemia in the same condition (1). Furthermore, lower mortality rates have been observed in hyperglycaemic patients presenting with acute myocardial infarction receiving insulin therapy (2). Protocols for regulation of glucose levels on high care and intensive care facilities have been introduced in many hospitals. However, compliance to such protocols may be inadequate, especially when other treatments interfere with the timing of measurements and/or time to calculate new insulin infusion rates. The use of a computerized clinical decision support system (CDSS) for glucose regulation was shown to improve both protocol adherence and achievement of glycemic targets when compared to a paper guideline in a mixed surgical / medical intensive care unit (3). Prior to the current study, glucose levels at our Intensive Cardiac Care Unit (ICCU) were inadequately controlled, and adherence to the existing paper protocol was suboptimal. Therefore, a web based CDSS for glucose control was developed (4,5).

The initial CDSS consisted of an automated version of the existing paper protocol. A touch-screen monitor on the ICCU displays a board view of all currently admitted patients. New glucose values are automatically retrieved from the laboratory and displayed along with insulin infusion rates and patient data from the Patient Data Management System (PDMS). For each new glucose value, a pop-up is displayed with an advice for adaptation of the insulin infusion rate and timing of the next glucose measurement as appropriate. Temporal trends in glucose levels and insulin dosage are displayed as an additional aid. Following implementation, improvements were observed in protocol compliance and achievement of glycemic targets, but there was ample room for further improvement. Using feedback from nurses, physicians and new evidence from literature, two modifications of the CDSS protocol were made [1.] to account for a decrease in glucose levels over time and [2.] widening of glucose target levels as well as addition of a mealtime protocol since implementation of the CDSS. The aim of the current study was to evaluate the impact of these protocol modifications on protocol compliance and achievement of target glucose levels in the ICCU.

METHODS

Study design and setting

Data was collected for patients with two or more glucose measurements in the period following the implementation of the CDSS (28 July until 30 November 2008: group 1, 269 patients); in the period after the first and before the second protocol modification (1 December 2008 until 22 November 2009: group 2, 814 patients); and after the second modification (23 November 2009 until 31 January 2010: group 3, 142 patients).

The study was conducted at the ICCU of the Erasmus University Medical Center in Rotterdam, the Netherlands. The unit consists of 8 beds with a 1:1-1:2 nurse to patient ratio and 1400-1700 admissions per year. Patients admitted included cardiac, non-surgical patients requiring intensive (cardiac) care. The nursing staff uses a web-based PDMS (Chart-Assist, Draeger Medical, Andover, MA).

Insulin protocol characteristics and modifications

Protocol 1

During the first study period, a simple sliding scale protocol with a target glucose range of 4.5-7.0 mmol/l (81-126 mg/dl) was used. Copies of the protocol were available at the bedside of each patient and at the main ICCU desk. An excerpt of the protocol is given in Figure 1a. The protocol was nurse-driven, and initiated for all patients with an acute myocardial infarction or with a history of diabetes; for all other patients with elevated glucose levels a physician was consulted first. For each glucose value, the protocol provided an advice regarding the subsequent insulin infusion rate and the time of the next measurement. The glucose level was determined in the hospital central laboratory from a venous or arterial blood sample.

Protocol 2

Based on user feedback from the first period (nurses were asked to register reasons for non-compliance in the PDMS), changes were made to the protocol to manage insulin therapy in the case of decreasing glucose levels. This modification aimed to prevent hypoglycaemic episodes and facilitate achievement of a more stable normoglycemic state. In the case of decreasing glucose values, the protocol advised more frequent measurements and/or a decrease in insulin dosage. The modifications were made to the CDSS and the paper copies. Nurses were informed of the changes by a newsletter and plenary as well as individual instructions.

Protocol 3

The user feedback from the second period revealed that the protocol did not account for increased insulin demands around mealtimes, in patients allowed and capable of eating. Therefore, a separate protocol was developed regarding the administration of insulin around mealtimes. As the necessary information regarding nutrition was not available in the PDMS, this specific protocol was used as a paper version only.

In addition to the advice regarding the administration of insulin around meals, the new protocol also applied a higher threshold for initiating insulin therapy (10.1 instead of 7.1 mmol/l). Furthermore, the target range was widened (from 4.5 – 7.0 to 4.1 – 8.0 mmol/l). This was done following the results of the NICE-SUGAR trial which demonstrated

Table 1: Characteristics of protocols used during the study period

Protocol characteristics	Protocol 1	Protocol 2	Protocol 3
Electronic	yes	yes	yes
Paper supplement	no	no	yes
Glucose threshold for initiating insulin (mmol/l)	7	7	10
Target glucose range (mmol/l)	4.5 - 7	4.5 - 7	4 - 8
Mealttime insulin adjustment	no	no	yes
Accounts for decrease in glucose levels during insulin therapy	no	yes	yes

Initial glucose value	Start Insulin Infusion at	remeasure
>20 mmol/l	5 units/hour, notify physician	in 1 hour
17.1-20.0	4 units/hour	in 1 hour
14.1-17.0	3 units/hour	in 1 hour
11.1-14.0	2 units/hour	in 1 hour
7.1-11.0	1 units/hour	in 1 hour
<7.1	no insulin	in 4 hours

Next glucose value	Insulin infusion	remeasure
>11.0	ask physician about increase	in 2 hours
7.8-11.0	increase with 1 unit/hour	in 2 hours
7.1-7.8	increase with 0.5 unit/hour	in 2 hours
4.5-7.0	do not change	in 4 hours

In case of hypoglycemia	Insulin infusion	remeasure
3.3 - 4.4	decrease infusion rate by 50%	in 1 hour
2.2 - 3.2	stop insulin infusion, ensure sufficient glucose intake	in 1 hour
<2.2	stop insulin infusion, administer 10g glucose intravenously	< 1 hour

Figure 1a: Excerpt from the insulin protocol as used during the first study period.

no additional benefit to strict glycemic regulation (6). Excerpts from protocol 3 are given in figure 1b (continuous insulin infusion) and 1c (mealttime insulin). An overview of the different protocol characteristics is given in Table 1.

Glucose Clinical Decision Support System (CDSS)

The design of the CDSS for glucose control has been described in detail elsewhere (4,5,7). Briefly, using a touch-screen, a board view display was developed showing all eight ICU beds. Glucose values are represented for each bed by colored bars; bars are green when the value is within the target range, and red when too high or too low. The insulin infusion rate is represented by a black line. Bars are displayed for measurements over the last 15 hours. When a new glucose value is reported by the lab, a pop-up is displayed with the value and an algorithm-generated advice with respect to the adjustment in insulin infusion rate and the time for the next glucose measurement. This algorithm is based on the glucose protocols as described above. The pop-up can be closed with a finger press. Additionally, the last pop-up can be recalled by touching the patient name. The glucose value and insulin infusion rate at a given time can be retrieved by touching the respective bar.

Patients without insulin infusion

Initial glucose value	Start Insulin Infusion at	remeasure
>20 mmol/l	5 units/hour, notify physician	in 1 hour
17.1-20.0	4 units/hour	in 1 hour
14.1-17.0	3 units/hour	in 1 hour
11.1-14.0	2 units/hour	in 1 hour
10.1-11.0	1 unit/hour	in 1 hour
4.1-10.0	no insulin	in 4 hours

Patients with insulin infusion

Decrease <25% or increase in glucose from previous measurement		
Glucose	Insulin infusion	remeasure
>14.0	ask physician about increase	in 2 hours
10.1-14.0	increase with 1 unit/hour	in 2 hours
8.1-10.0	increase with 0.5 unit/hour	in 2 hours
5.1-8.0	do not change	in 4 hours
4.1-5.0	decrease by 50% and notify physician	in 1 hour
Decrease 25-50% in glucose from previous measurement		
Glucose	Insulin infusion	remeasure
>11.0	do not change	in 1 hour
4.1-11.0	decrease by 50% and notify physician	in 1 hour
Decrease >50% in glucose from previous measurement		
Glucose	Insulin infusion	remeasure
>5.0	decrease by 50% and notify physician	in 1 hour
4.1-5.0	stop insulin and notify physician	in 1 hour

Hypoglycemia (glucose < 4.1): notify physician!

Glucose	Insulin infusion	remeasure
>4.0	ask physician about restarting insulin	in 1 hour
3.2 - 4.0	stop insulin infusion	in 15 minutes
<3.2	stop insulin infusion, administer 5g glucose intravenously	in 15 minutes

Figure 1b: Excerpt from the insulin infusion protocol for as used in the final study period.

Mealtime insulin guideline

Insulin for patients consuming meals	
▶ Insulin dependent diabetics => consult physician	
▶ Patients with insulin infusion => use diagram to calculate insulin bolus	
▶ Patients without insulin infusion and preprandial glucose >10 => start Insulin according to protocol and administer bolus according to diagram	
▶ No insulin infusion and preprandial glucose <10 => no insulin bolus!	
Diagram for mealtime insulin bolus	
Directly postprandial:	
Administer 4 units of insulin (<i>adjust for amount eaten and insulin required at previous meals</i>)	
Measure glucose 1 hour AFTER meal:	
Glucose <4.1	see protocol for hypoglycemia
Glucose 4.1-10.0	no action
Glucose 10.1-12.0	administer an additional 2 units insulin
Glucose 12.1-14.0	administer an additional 4 units insulin
Glucose >14	consult physician for additional insulin

Figure 1c: Excerpt from the guideline for the mealtime insulin bolus as used in the final study period

Patient data, glucose values and insulin infusion rates are automatically retrieved from the PDMS. A 15-inch touch screen integrated PC was used for the interface, and mounted behind the nurse's desk, easily accessible and clearly visible to all nurses.

Data collection

Patient demographics, admission diagnoses and medical history were registered in the PDMS. Glucose values were registered in the hospital information system. Insulin infusion rates and reasons for not complying with the protocol were retrieved from the PDMS. For each patient, the average glucose during admission was calculated (using the area under the curve methodology with linear interpolation (8)). Hypoglycaemic episodes were defined as any value lower than 4.0 mmol/l; severe hypoglycaemia was defined as any value lower than 3.3 mmol/l. Protocol compliance with respect to the timeliness of measurement was determined as the proportion of measurements done within the advised time from the previous measurement, with a 10% margin. Protocol compliance with respect to insulin dosage was determined using the difference between the actual insulin infusion rate and the recommended rate between the glucose measurement generating the advice and the subsequent measurement. Evaluation of timeliness was done for all measurements except for the first; evaluation of correct insulin dosage was done for all measurements except for the last. Reasons for non-compliance were collected and stored in a database. First, nurses were instructed to enter the reason for deviation from the protocol into the electronic charting system, they could also choose to write down comments in a notebook present next to the touch-screen. The study investigator (JL) was available for consultation on weekdays and by phone over weekends and nights to answer questions and receive feedback.

Statistical analysis

Statistical analysis was done with SPSS 15.0 (Chicago, USA). Continuous data were expressed as mean with Standard Deviation (SD) or median values with interquartile range (IQR), as appropriate. Student's t-test and analysis of variance were used to analyze continuous data between the groups. Differences between proportions were compared using the χ^2 test. $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

During the study period, glucose was measured in 1898 patients; 1225 had at least two measurements during admission and were included in the study; 269 in group 1; 814 in group 2 and 142 in group 3. Patient characteristics are shown in Table 2. Age was 64 ± 14 years. The proportion of males was slightly higher in group 1 vs. group 2 (72 vs. 64%,

P=0.02) and group 3 (72 vs. 62%, P = 0.051), also the proportion of patients with renal disease was higher in group 1 vs. groups 2 and 3 (14% vs. 9% and 8%, P=0.04). There were more diabetics and patients with previous myocardial infarction, and less patients with heart failure in groups 2 and 3 vs. group 1, however these differences did not reach statistical significance.

Clinical characteristics are shown in Table 3. Overall, 53% of the patients were admitted for evaluation of an acute coronary syndrome. A diagnosis of acute myocardial infarction was established in 35% of the patients. From groups 1 to 3, an increase was seen in the percentage diagnosed with stable angina and cardiac arrest, and a decrease in heart failure and valvular disease although the overall APACHE-2 score as a measure of disease severity did not change. Duration of admission, admission glucose levels, number of glucose measurements and average glucose during admission were similar across the groups.

Table 2: Baseline characteristics of patients included in the analysis

Baseline characteristics	All (1225)		Group 1 (269)		Group 2 (814)		Group 3 (142)		
Variable	value	n	value	n	value	n	value	n	
Age (years)	64 ± 15		63 ± 14		64 ± 15		64 ± 14		P = NS
% male	66%		72%		64%		62%		P = 0.051
Body mass index (kg/m ²)	27.2 ± 14	846	26.5 ± 4		27.2 ± 16		28.2 ± 15		P = NS
Previous disease									
Diabetes	21%	255	19%	50	21%	170	25%	35	P = 0.4
Hypertension	32%	394	35%	93	31%	255	32%	46	P = 0.6
Myocardial infarction	22%	273	21%	56	22%	179	27%	38	P = 0.4
PCI	17%	210	18%	48	17%	141	15%	21	P = 0.7
CABG	10%	127	11%	30	10%	83	10%	14	P = 0.9
CVA/TIA	10%	125	10%	28	11%	87	7%	10	P = 0.4
Renal disease	10%	124	14%	38	9%	75	8%	11	P = 0.04
Heart failure	16%	192	15%	41	17%	135	11%	16	P = 0.3
Angina	13%	155	12%	31	14%	111	9%	13	P = 0.3
Vascular disease	8%	102	7%	20	9%	72	7%	10	P = 0.6
COPD	9%	111	7%	20	10%	79	9%	12	P = 0.5

PCI (percutaneous coronary intervention); CABG (Coronary Artery Bypass Graft surgery); CVA/TIA (Cerebrovascular event); COPD (Chronic pulmonary disease). Values are displayed as mean ± Standard Deviation.

Glucose levels

Average glucose levels during admission are displayed by group in Figure 2. As could be expected, based on the protocol modifications, there was a trend towards higher glucose levels from Group 1 to 3. The proportion of patients with an average glucose within the "normal" range (<8 mmol/l) was lower in groups 2 and 3 (P<0.001). There was also a decrease in the incidence of hypoglycaemic events over time, however this trend did not reach statistical significance. The incidence of severe hypoglycaemia (<3.3 mmol/l) was low in all groups (<1.2%).

Table 3: Clinical characteristics of patients included in the analysis

Clinical characteristics	All (1225)		Group 1 (269)		Group 2 (814)		Group 3 (142)		P
	value	n	value	n	value	n	value	n	
Admission diagnosis									
Suspected ACS	53%	650	55%	149	52%	423	55%	78	P = 0.55
Other	47%	575	45%	120	48%	391	45%	64	
Discharge diagnosis									
Myocardial infarction	35%	424	36%	98	34%	277	35%	49	P = 0.06
Unstable angina	13%	153	14%	38	12%	98	12%	17	
Stable angina	5%	58	3%	7	5%	39	9%	12	
Cardiac arrest	11%	132	6%	15	12%	95	16%	22	
Heart failure	13%	157	14%	38	13%	107	9%	12	
Arrhythmia	7%	83	6%	16	7%	58	6%	9	
Valvular disease	7%	81	7%	19	7%	56	4%	6	
Procedure related	4%	48	5%	14	4%	30	3%	4	
Other	7%	89	9%	24	7%	54	8%	11	
Admission duration (days)	1.03 (0.57 - 2.74)		1.01 (0.63 - 2.74)		1.04 (0.56 - 2.7)		1.14 (0.5 - 2.92)		P = NS
APACHE-2 score	15 (11 - 23)	1128	16 (12 - 25)	248	15 (11 - 22)	745	16 (12 - 27)	135	P = NS
Glucose measurements (n)	6 (3 - 16)		6 (3 - 16)		6 (3 - 15)		6 (3 - 17)		P = NS
Admission glucose	8.3 (6.6 - 11.0)		8.2 (6.6 - 11.0)		8.3 (6.6 - 11.2)		8.9 (7.0 - 10.8)		P = NS
Glucose during admission	7.3 (7 - 8)		7.2 (6.5 - 8.4)		7.3 (6.7 - 8.4)		7.5 (6.6 - 8.8)		P = NS
< 8 mmol/l	66%	813	70%	187	66%	540	61%	86	P < 0.001
8 - 10 mmol/l	22%	270	20%	54	22%	180	25%	36	
> 10.0 mmol/l	12%	142	10%	28	12%	94	14%	20	
Hypoglycemia									
<3.3 mmol/l	1.0%	192	1.1%	46	1.1%	130	0.6%	16	P = 0.07
3.3-4.0 mmol/l	1.7%	334	2.6%	111	1.6%	194	1.2%	29	

ACS (Acute coronary syndrome); APACHE (Acute Physiology and Chronic Health Evaluation). Values are displayed as mean ± Standard deviation or median (25 - 75 percentile) as appropriate.

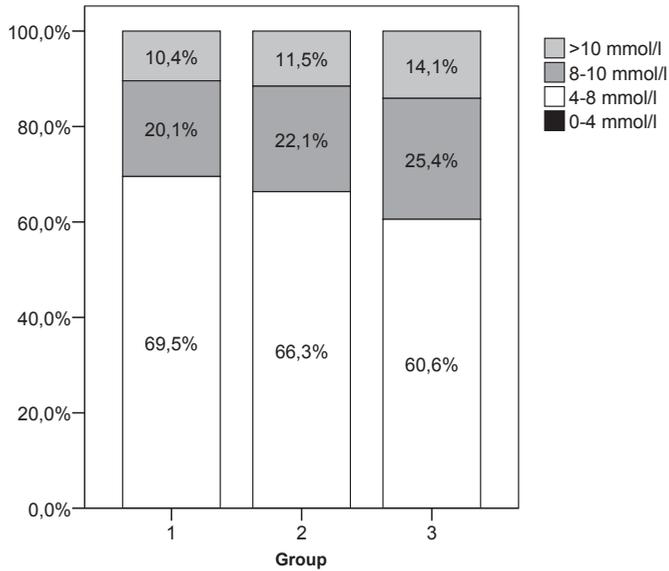
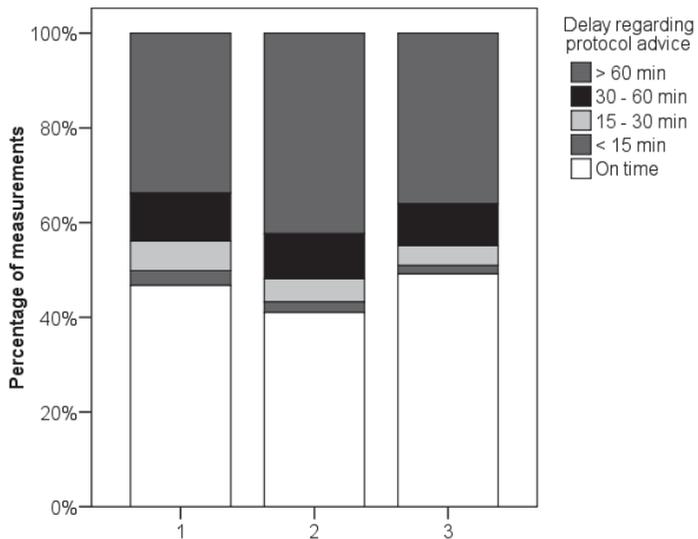


Figure 2: Average glucose levels during admission for patients over the three glucose protocols



Measurement	Group 1		Group 2		Group 3	
	%	n	%	n	%	n
On time	46,7%	1877	41,0%	4738	49,2%	1164
< 15 min	3,1%	126	2,2%	253	1,7%	41
15 - 30 min	6,2%	250	4,9%	563	4,2%	99
30 - 60 min	10,2%	408	9,6%	1103	8,9%	210
> 60 min	33,8%	1356	42,3%	4887	36,0%	853

P<0.001

Figure 3: Compliance with timing of glucose measurements according to the protocol instructions.

Protocol adherence

In total, 19,153 measurements were analyzed (17,928 after omission of the first and last measurement for evaluation of timeliness and insulin dosage respectively). The number of measurements per patient was slightly higher in group 3 compared to groups 1 and 2 (16.7 vs. 14.5; $P=NS$). Compliance to the insulin protocol with respect to timeliness of the glucose measurement was highest with protocol 3 and lowest with protocol 2 (52% vs. 44%, $P < 0.001$, figures 3 and 4). Compliance with the recommended insulin dosage was highest for protocol 3 and lowest for protocol 2 (71% vs. 57%, $P < 0.001$).

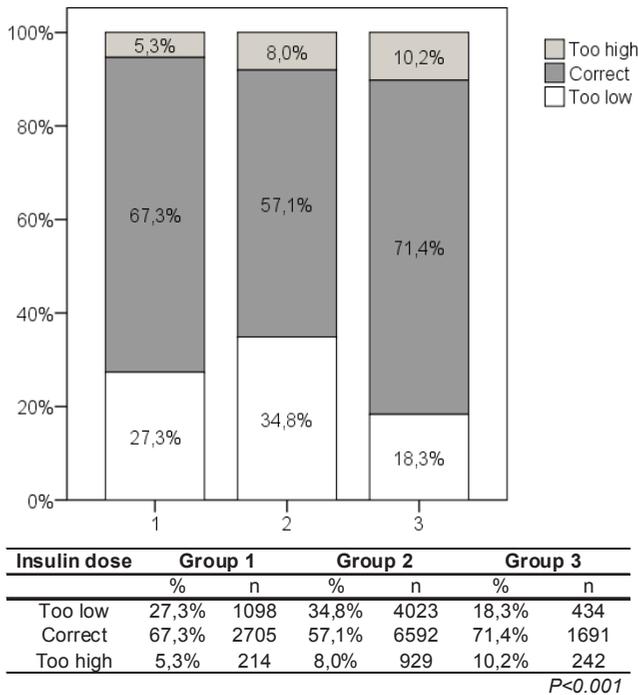


Figure 4: Compliance with insulin dosage according to the protocol instructions.

Deviation from protocol advice

Nurse-reported reasons for deviating from the protocol advice (either time of measurement or dosage of insulin) are displayed in Table 4. The reporting incidence as percentage of the total number of glucose measurements decreased from 3.3% in group 1 to 2.0% and 0.9% in groups 2 and 3 respectively. Overall, changes in nutrition were the most frequent reason for declination: less intake or stopping of enteral feeding during the night (15.3%), a change in enteral feeding (10.0%) and meals (9.5%). Deviation to account for a decrease in glucose values was reported more frequently for protocol 1 than for protocols

2 and 3. The most frequent reported reasons for deviating from protocol 3 were highly variable glucose levels and night-time changes in nutrition; no deviations were reported to accommodate for meals and/or a decrease in glucose levels in this group.

Table 4: Nurse-reported reasons for non-compliance with protocol advice

	All (379)		Group 1 (131)		Group 2 (228)		Group 3 (20)	
<i>n as percentage of all measurements</i>	2.0% (379/19153)		3.1% (131/4286)		1.8% (228/12358)		0.8% (20/2509)	
Reason	%	n	%	n	%	n	%	n
Nutrition related								
Nighttime	15%	58	12%	16	16%	37	25%	5
Change in nutrition	10%	38	13%	17	9%	21		
Mealtime	9%	36	7%	9	12%	27		
Other reasons								
Physician's order	12%	46	14%	18	12%	27	5%	1
Decrease in glucose	9%	35	18%	24	5%	11		
Procedure	8%	32	3%	4	12%	27	5%	1
Variable glucose	7%	28	8%	10	6%	13	25%	5
Bolus needed	6%	22	5%	6	6%	14	10%	2
Hyper/hypokalemia	4%	17	2%	3	6%	13	5%	1
Own medication	4%	15	3%	4	4%	10	5%	1
Blood sampling / IV issues	3%	12	3%	4	3%	6	10%	2
Ineffective insulin batch	1%	5			2%	5		
Stable glucose	1%	4	2%	3	0%	1		
Miscellaneous	8%	31	10%	13	7%	16	10%	2

IV (Intravenous access)

DISCUSSION

We hypothesized that the modifications to the protocols would lead to an increase in number of patients with an average glucose in the “normal” range (<8 mmol/l), and an increase in protocol compliance. Deviation from the protocol advice in the first protocol occurred in more than a third of the instances: a main reason was to prevent hypoglycaemia when glucose levels were decreasing. Therefore the first modification was to manage decreasing glucose levels by advising lower insulin dosages and more frequent measurements to reduce the risk of hypoglycemia. The incidence of hypoglycemia was indeed lower in group 2 vs. group 1, although this did not reach statistical significance. However, the lower insulin dosages, in combination with more frequent measurements resulted in more detected hyperglycemic episodes. Also, the workload for nurses increased, which can explain the lower compliance with protocol 2 vs. protocol 1, especially regarding the timeliness of the measurements.

After implementation of the second protocol, the most frequent reason for deviation was to regulate glucose levels around mealtimes. Therefore, in protocol 3 we introduced

a specific insulin protocol to improve glucose regulation around mealtimes. Indeed, the reporting incidence of protocol deviation in the last group was lower, and compliance was higher, indicating that this protocol best fit the nursing workflow. Also in the third protocol, a higher glucose threshold for initiating insulin treatment was used of 10 mmol/l instead of 8 mmol/l, and the target range was widened from 4.5 - 7 mmol/l to 4 to 8 mmol/l. These changes were made following the results of the NICE-SUGAR trial (6) and subsequent modifications in the ACC-STEMI guidelines (9). These changes explain the higher glucose levels and fewer hypoglycemic episodes in the final study group.

This study describes a “real-life” experience of modifying a computerized ICCU insulin protocol to improve glucose regulation and compliance and demonstrates that achieving glucose control is challenging indeed. Several factors make it difficult to design a uniform protocol for all patients: ideally one would design different protocols for intubated / non intubated patients, for those receiving no food, enteral feeding and normal intake, for patients with or without insulin dependent diabetes. In addition to these factors, the severity of disease in ICCU patients varies greatly and many patients recover over time which provides an additional challenge for optimal glucose management. Although the goals of the protocol modifications are reached, at least in part, in the presented study, the changes are subtle and take time to become apparent.

Computerized insulin protocols for glycemic control

Many different glucose protocols exist for the intensive care setting and have been reviewed extensively (10,11). The CDSS interface in our study was well accepted by the nurses: the visibility was good and improved the awareness to new glucose values once these became available from the laboratory. Although the protocols previously studied varied in design of decision support systems, type of intensive care unit and glycemic outcome measures, most studies report an improvement in glycemic parameters as the result of an automated protocol. However, most of these studies were done in a more uniform patient population (3,12). The current study describes a unique, diverse ICCU population consisting of patients experiencing complications after admission for an acute coronary syndrome or other acute cardiac condition, and patients referred from other hospitals for specialized care. Patients with uncomplicated clinical procedures are admitted to the medium care ward or are discharged to the referring center. Our experience shows that it is difficult to establish a protocol that is applicable to all patients at in many different circumstances.

Design of mealtime insulin protocol

Managing insulin therapy for patients around mealtimes is challenging and should depend on individual insulin sensitivity as well as meal composition. Although protocols exist (13,14), they proved either to be unsuitable for the ICCU setting or required additional

information, not available electronically in the PDMS or charting system. The protocol in group 3 accounts for insulin dosages around mealtimes, but does not do so automatically. The mealtime instructions are displayed on the glucose CDSS touchscreen, but as mealtimes and amount consumed vary by patient, and as this information is not available electronically, this information could not be implemented in the CDSS. Though manual input would be possible to calculate the required insulin dose, the problems associated with data entry errors (15) could well reduce or eliminate the potential benefit of the extra information.

Importance of glucose regulation

Several clinical studies have addressed the relation between glucose lowering therapy and outcomes, however the results are not fully consistent. The first DIGAMI trial demonstrated a significantly reduced mortality at 1 year in patients with an acute myocardial infarction treated with an intensive insulin regimen (16). The Leuven study found a similar beneficial effect of intensive insulin therapy on mortality in intensive care patients (17). More recent studies, however, were unable to reproduce these effects and illustrate the difficulties in achieving tight glycaemic targets (6,18). The DIGAMI-2 study did not achieve the expected difference in glucose levels between groups of patients allocated to intensive or less intensive insulin therapy and thus did not demonstrate a clinical advantage of the intensive insulin therapy (18). In contrast, the NICE-SUGAR study did achieve lower glucose levels in the intervention group, but at the cost of more hypoglycaemic episodes (6). These studies illustrate the difficulties of implementing an insulin protocol and maintaining compliance with it, and fuel the uncertainty around the optimal insulin treatment strategy and the optimal glucose target levels.

Future directions

Optimal glycaemic targets for ICU patients remain undecided. The initial studies by Malmberg et al. (16) and Van den Berghe et al. (17) showed a survival advantage for tight glycaemic control (4 - 6mmol/l). However, later studies including DIGAMI 2 (18) and NICE-SUGAR (6) reported increased incidence of hypoglycaemia, and in the case of the NICE-SUGAR trial, an increased mortality in the group with tight glycaemic control. Accordingly, the current ACC/AHA guidelines for management of acute myocardial infarction (9) advise a threshold of 10 mmol/l for initiating glucose lowering therapy; and this advice was implemented in the most recent modification of our protocol. Further work is needed to determine optimal glucose targets for the intensive cardiac care setting. Furthermore, the method for glucose measurement can be improved. During the study period, measurements were taken from venous and arterial blood samples, and sent to the laboratory for analysis. This resulted in a delay of 5-25 minutes between time of sampling and the result. The laboratory determination is more accurate than point of care systems, but this

advantage may be lost due to the delay and point-of-care measurement may therefore be more appropriate. Ultimately, a closed loop system using a continuous glucose sensor coupled to an algorithm driven insulin pump might provide optimal glycemic regulation. However, even though the accuracy of glucose sensor devices is high, even in the intensive care setting (19,20), there is a risk of undetected hypoglycaemia (21), especially when subcutaneous perfusion is compromised in patients with heart failure or in shock. An intravenous glucose sensor might be more appropriate, as it would not be affected by impaired skin perfusion, but no such system is currently commercially available.

CONCLUSION

Stepwise modification of the ICCU insulin protocol resulted in an increase in protocol compliance with regard to timing of glucose measurements and better adherence to the advised insulin dosage. The percentage of patients achieving a mean glucose level <8mmol/l however, did not increase, illustrating the difficulty in regulating glucose in the ICCU setting. Further work is needed to develop and validate better protocols for blood glucose regulation in the ICCU. A reliable, continuous glucose measurement system may be of great value in this setting.

REFERENCES

1. Penfold S, Gouni R, Hamilton P, Richardson T, Kerr D. Immediate in-patient management of hyperglycaemia-confusion rather than consensus? *QJM*. 2008 Feb;101(2):87-90.
2. Weston C, Walker L, Birkhead J. Early impact of insulin treatment on mortality for hyperglycaemic patients without known diabetes who present with an acute coronary syndrome. *Heart*. 2007 Dec;93(12):1542-6.
3. Rood E, Bosman RJ, van der Spoel JI, Taylor P, Zandstra DF. Use of a Computerized Guideline for Glucose Regulation in the Intensive Care Unit Improved Both Guideline Adherence and Glucose Regulation. *J Am Med Inform Assoc*. 2005 Mar 1;12(2):172-180.
4. Barendse R, Lipton J, van Ettinger M, Nelwan S, van der Putten N. Implementing a Clinical Decision Support System for Glucose Control for the Intensive Cardiac Care [Internet]. In: *Artificial Intelligence in Medicine*. 2009 [cited 2009 Sep 30]. p. 161-165. Available from: http://dx.doi.org/10.1007/978-3-642-02976-9_21
5. Lipton JA, Barendse, Eenkhoorn, van der Ende, van Dam, van Ettinger, et al. Glucose control as a model for implementation of a clinical decision support system [Internet]. [cited 2009 Mar 11]; Available from: <http://www.cinc.org/Proceedings/2008/pdf/0661.pdf>
6. The NICE-SUGAR Study Investigators. Intensive versus Conventional Glucose Control in Critically Ill Patients. *N Engl J Med*. 2009 Mar 26;360(13):1283-1297.
7. Jonathan A. Lipton, Rogier Barendse, Stefan Nelwan, Dam TV, Maarten van Ettinger, Niek van der Putten. Protocol Adherence on the Cardiac Intensive Care Unit: Glucose Control as a Model for Implementation of Clinical Decision Support [Internet]. In: *CINC 2008*. Bologna: 2008 [cited 2009 Mar 2]. Available from: <http://www.cinc.org/Proceedings/2008/pdf/0661.pdf>
8. Le Floch JP, Escuyer P, Baudin E, Baudon D, Perlemuter L. Blood glucose area under the curve. Methodological aspects. *Diabetes Care*. 1990 Feb;13(2):172-5.
9. Kushner FG, Hand M, Smith SC, King SB, Anderson JL, Antman EM, et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update). A Report of the American College of Cardiol-

- ogy Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* [Internet]. 2009 Nov 18 [cited 2009 Dec 1]; Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19923169>
10. Meijering S, Corstjens A, Tulleken J, Meertens J, Zijlstra J, Ligtenberg J. Towards a feasible algorithm for tight glycaemic control in critically ill patients: a systematic review of the literature. *Critical Care*. 2006;10(1):R19.
 11. Van Herpe T, De Moor B, Van den Berghe G. Towards closed-loop glycaemic control. *Best Pract Res Clin Anaesthesiol*. 2009 Mar;23(1):69-80.
 12. Vogelzang M, Loef BG, Regtien JG, van der Horst ICC, van Assen H, Zijlstra F, et al. Computer-assisted glucose control in critically ill patients. *Intensive Care Med*. 2008 Aug;34(8):1421-7.
 13. The Portland Protocol [Internet]. [cited 2009 Dec 31]; Available from: http://www.providence.org/oregon/programs_and_services/heart/portlandprotocol/default.htm
 14. de Mulder M, Zwaan E, Wielinga Y, Stam F, Umans VAWM. How to implement a clinical pathway for intensive glucose regulation in acute coronary syndromes. *Crit Pathw Cardiol*. 2009 Jun;8(2):72-78.
 15. Sward K, Orme Jr. J, Sorenson D, Baumann L, Morris A. Reasons for declining computerized insulin protocol recommendations: Application of a framework. *Journal of Biomedical Informatics*. 2008 Jun;41(3):488-497.
 16. Malmberg K, Rydén L, Efendic S, Herlitz J, Nicol P, Waldenström A, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J. Am. Coll. Cardiol*. 1995 Jul;26(1):57-65.
 17. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in the critically ill patients. *N. Engl. J. Med*. 2001 Nov 8;345(19):1359-1367.
 18. Malmberg K, Rydén L, Wedel H, Birkeland K, Bootsma A, Dickstein K, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur. Heart J*. 2005 Apr;26(7):650-661.
 19. Logtenberg SJ, Kleefstra N, Snellen FT, Groenier KH, Slingerland RJ, Nierich AP, et al. Pre- and postoperative accuracy and safety of a real-time continuous glucose monitoring system in cardiac surgical patients: a randomized pilot study. *Diabetes Technol. Ther*. 2009 Jan;11(1):31-37.
 20. Holzinger U, Warszawska J, Kitzberger R, Herkner H, Metnitz PGH, Madl C. Impact of shock requiring norepinephrine on the accuracy and reliability of subcutaneous continuous glucose monitoring. *Intensive Care Med*. 2009 Aug;35(8):1383-1389.
 21. Rabiee A, Andreasik RNV, Abu-Hamdah R, Galiatsatos BSP, Khouri Z, Gibson BR, et al. Numerical and clinical accuracy of a continuous glucose monitoring system during intravenous insulin therapy in the surgical and burn intensive care units. *J Diabetes Sci Technol*. 2009;3(4):951-959.

Summary and
discussion

Samenvatting en
discussie

SUMMARY AND DISCUSSION

The quality of care in acute cardiac disease has improved dramatically. Simultaneously, the use of information technology for data storage and retrieval, for monitoring and for clinical decision support in health care has increased. **Chapter 1** describes the concept of clinical decision support systems (CDSS), information systems that select relevant patient-specific data and presenting these so the caregiver can make a “better” diagnostic or treatment decision. In a complex clinical environment such as the intensive care, decisions are made using data originating from many different electronic sources. A CDSS uses this information to provide workflow, diagnostic and treatment support. A CDSS can improve adherence to guidelines, and also provide data to aid developments of new, improved guidelines. CDSS have the potential to perform an important role in evidence-based medicine. However, the implementation of a CDSS can lead to unexpected outcomes (1). For example, workflow could be altered in a way that increases the delay in administering medication (2). A successful implementation of a CDSS should include a design that fits into the clinical workflow. Also a careful evaluation of its utilization as well as an evaluation of clinical outcomes before and after implementation of the CDSS should be done.

In patients with evolving myocardial infarction (AMI), rapid treatment improves outcome: any unnecessary delay in time to treatment should be avoided (3,4). **To establish the diagnosis** of AMI, the electrocardiogram (ECG) provides essential information. Accordingly, the ECG is the cornerstone in the triage of patients with chest pain. **Chapter 2** describes the ability of paramedics to detect ST-elevation AMI. In ECG's collected from 121 patients that the paramedics classified as ST-elevation AMI, the diagnosis was confirmed in 49%. The true-positive rate was 60% in patients that had an ECG without confounders and 37% in ECG's with confounders such as bundle branch block, prior AMI and left ventricular hypertrophy. By contrast, when the ECG's were interpreted by an experienced cardiologist, the true-positive rate was 88% and was not affected by the presence of ECG confounders. The results of this study emphasize the importance of education and training of paramedics in the acquisition and interpretation of ECG's, especially in the presence of confounders. Also, they support initiatives to transmit pre-hospital ECG's directly to a cardiologist. **Chapter 3** presents a methodology for implementing a transmission system for ECG's from the pre-hospital setting. The system transmits the ECG from the ambulance to a central computer system. When received, the on-call cardiologist is notified. The cardiologist can access the ECG using a handheld digital device (such as a PDA or “smart”-phone), and establish contact with the paramedics. He can then give instructions regarding thrombolytic treatment or have them transport the patient directly to a hospital with facilities for primary PCI, thus reducing treatment delay. Based on the experience of implementing this system in Guilford County, North-Carolina, we make several recommendations. First, the commu-

nity needs to have a well-organized emergency medical service (EMS) with paramedics that are able to acquire 12-lead ECG's. The EMS needs to be technically equipped to transmit the ECG's and have the resources to test, introduce and maintain it. Furthermore, the participating hospitals must provide reperfusion therapy on a 24/7 basis. Finally, a study coordination center should oversee the implementation and evaluation of the technology. To successfully proceed with the implementation, we proposed a stepwise approach in three phases. In phase one the technology is chosen and tested clinically, protocols for treatment and communication are established and baseline data regarding time to treatment is collected. In phase two the testing of the system is completed, necessary adjustments are made to the treatment, communication and data collection protocols, and data collection is started. In phase three, the system is implemented, allowing cardiologists to make pre-hospital treatment decisions, while the incoming data is monitored carefully to ensure patient safety.

Chapter 4 presents the implementation of such a system in Cabarrus County, North Carolina. Paramedics acquired 12-lead ECG's and utilized a pocket PC, linked to the monitor, to transmit the ECG's to a computer at the emergency department. A nurse at the emergency department then sent the ECG to the on-call cardiologist, who could view it on a pocket PC and give instructions to bypass the emergency department and bring the patient directly to the cath-lab for reperfusion therapy. We presented five cases demonstrating the ability of the system to function and achieve reperfusion within 35 minutes from admission to the hospital. The design of TIME NE is presented, a trial set up to evaluate the effectiveness of pre-hospital transmission of ECG's to reduce time to reperfusion. This trial (5) included 192 patients, 48 in a historical control group and 144 in the intervention period. The lowest door to reperfusion time was seen in patients transported by ambulance with a successfully transmitted ECG: 50 (30 – 66) minutes. In patients where transmission was not successful, the time to reperfusion was 78 (64 – 209) minutes, but was still shorter than the 101 (80 – 132) minutes in patients transported by ambulance in the historical control group. A major limitation of the technology was a limited coverage of wireless networks, disabling the reading of the ECG's by the cardiologist. To a lesser extent, transmission of the ECG by paramedics was problematic, but improved with training.

A different approach to the pre-hospital triage of patients with chest pain is the use of an on-site computerized algorithm for ECG interpretation. Such system has been in use in Rotterdam since more than 20 years (6) and therefore not discussed in this thesis. Advantages of a system with using pre-hospital transmission to a cardiologist are a "gold-standard" evaluation of the ECG, with the highest possible accuracy, and the ability of the cardiologist to prepare for the patient's arrival. Dependability of such a system however is limited by the coverage of cell-phone and wireless networks. A pre-hospital evaluation by the paramedic is less dependent on technology, but requires training in ECG interpretation and results in a lower specificity when ECG confounders are present. A combined

Acute system, where only difficult-to-interpret ECG's are transmitted, could be an attractive third option.

Aside from the pre-hospital delay, in-hospital delays can be significant and are interesting targets for improvement. **Chapter 5** describes three interventions that were implemented within a 60-day period and resulted in a 39 ± 10 minute reduction in door to reperfusion time. The first intervention was a fast-track protocol for all patients with AMI in which a "cardiac alert" code was called, in which a pager message was sent automatically to the on-call cardiologist, the cath-lab coordinator, an ECG technician, a laboratory technician, a radiology technician, and the emergency department registration clerk. The second intervention was personalized feedback regarding time to reperfusion therapy on a quarterly basis to all cardiologists. The third intervention was to have an in-house cath-lab team 24-hours, 7 days a week (before: 7.00 to 19.00 on weekdays and on-call on all other hours). These interventions are examples of relatively simple, but effective measures to improve the care in acute cardiology by reducing the in-hospital treatment delay for patients with ST-elevation AMI.

Patients admitted to the Intensive Cardiac Care Unit (ICCU) are closely monitored by different devices that generate alarms when an abnormality is detected. However, most alarms do not signify a life-threatening event. **Chapter 6** describes 34,827 alarms collected over a four month period. Overall alarm frequency was 2.2 per patient per hour, but the alarms occurred in bursts: the interval between alarms was less than 90 seconds in half of the cases. Most alarms occurred during daytime and during times of increased patient care activity. This is logical as patient motion as well as a critical event is likely to trigger alarms over several monitored parameters. Also, during patient care procedures, artifacts of different monitored parameters are generated during a short period (for example motion artifacts during washing, and alarms when connecting or disconnecting a patient during admission and discharge).

The collection of alarms from different patient monitoring devices is challenging. In 1997, an initiative was started to improve information sharing between healthcare computer systems (7). In 2008 the alarm communication management profile (8) was proposed to establish interoperability between systems of different manufacturers for alarm messages. **Chapter 7** describes the implementation of this alarm communication profile at the Thoraxcenter of the Erasmus Medical Center, by developing the intelligent Patient Universal Tele-alarm (i-PUT). This open-source toolkit consists of different applications. The first and main application is the alarm manager, which can receive and distribute alarm messages to different configured disseminators (by e-mail, instant messaging, SMS and paging protocols). It also allows storage of the alarm messages in a database. A second application allows users to query the alarm database, providing insight into the frequency and type of alarm (as described in **chapter 6**). When implementing an alarm man-

agement system (such as i-PUT) in clinical practice, it is important to consider the effect on patient care. Disturbance of the clinical staff by devices like a pager, phone and/or PDA should be limited to instances when it is in the best interest of the patient. An increase of unnecessary alarms can lead to ignoring of alarms and to a delay in patient assessment. In addition to sending the alarm data to the relevant care provider, other information, such as laboratory values and CDSS-generated advice could be included to improve efficiency and quality of care. **Chapter 8** presents a web interface that gives access to the alarm data. This interface can be configured to display alarms for each patient bed or for an entire care unit. Clicking on an alarm displays the vital signs at the moment of the alarm, enabling the user to make an informed decision regarding further action. The web-based interface can be accessed from different "Smartphone" platforms, including i-Phone, Android, Windows Mobile and Blackberry.

Though the use of mobile devices to achieve faster, more adequate reaction to clinical alarms looks promising, it needs to be preceded by user-targeted interventions to reduce alarm frequency (such as avoiding 'over-monitoring' and inadequate alarm threshold settings). Only when the number of false alarms has been reduced and testing of the technology in a clinical setting is completed, can the effect of multimedia paging applications for improving patient care be evaluated.

Patients with AMI and diabetes mellitus, as well as patients admitted with elevated blood glucose without known diabetes, have impaired outcomes. Therefore, intensive glucose lowering therapy with insulin (IGL) has been proposed in diabetic- or hyperglycemic patients as it improves survival and reduces the incidence of adverse events. **Chapter 9** provides an overview of randomized controlled trials investigating the effect of IGL. We concluded that IGL targeted to achieve normoglycemia can improve survival and reduce incidence of adverse events. However, achievement of glucose regulation is difficult and carries the risk of hypoglycemia.

Systematic glucose-insulin-potassium infusion (GIK) has been proposed by Sodi-Palares et al (9) to prevent arrhythmias and to improve outcome after AMI. However, in spite of positive findings in some early studies, GIK did not show any beneficial effects in recent clinical trials, and thus this concept has been abandoned.

While IGL targeted to achieve normoglycemia can improve outcome in patients with AMI (10), achievement of glucose regulation is difficult and carries the risk of hypoglycemia (11,12). The prognostic value of hyperglycemia at or during admission in a particularly high risk group of patients, those admitted to the ICCU, is presented in **chapter 10**. Regression analysis was performed taking into account parameters of disease severity and other risk factors including age, gender, and prior (cardio) vascular and renal disease. Glucose at admission was measured in 1713 patients. A 1 mmol/l increase in admission glucose (above 9 mmol/l) was associated with 10% (95% CI 7% - 13%) increased risk for all

Acute cause mortality. In 893 patients with 3 or more measurements, a 1 mmol/l higher average glucose (above 8 mmol/l) was an additional independent predictor of mortality (hazard ratio 1.11, 95% CI 1.03 – 1.20).

Chapter 11 describes the compliance with the original paper protocol for regulating glucose that was in use at the ICCU. As compliance was low (only 37% of the measurements were done within the protocol advised time, and insulin was dosed according to the protocol in only 50% of the cases), we developed a CDSS for glucose control. Evaluation of the nursing workflow revealed important obstacles to protocol compliance: the absence of a notification of new laboratory results, low availability of the paper protocol and belief that adherence to the protocol would increase hypoglycemic episodes. A multidisciplinary approach using these findings led to a web-based CDSS for glucose control.

The CDSS, as described in detail in **chapter 12**, consists of a medical touch screen computer at the nurse desk which displays the 8 beds of the ICCU with patient characteristics, previous glucose measurements and insulin pump settings. When a new glucose value for a patient is determined, a popup appears on the “bed” of the corresponding patient. The popup displays the glucose value, time of measurement, generated advice regarding insulin treatment and advised time for the next glucose measurement. The CDSS stores the data for evaluation and is extendible to third-party rule engines that allow non-programmers to modify the decision rules using a graphic interface. We implemented the CDSS in clinical practice and evaluated the compliance with the protocol and glucose levels before and after implementation in **chapter 13**. A total of 667 patients were included: 425 before CDSS implementation and 242 after implementation. Implementation of the CDSS for glucose regulation in the ICCU resulted in an absolute 12% increase in protocol compliance with regard to timing of glucose measurements and administration of the advised insulin dosage. After implementation the percentage of patients with a mean glucose level within protocol target range (4.5 – 7 mmol/l) increased with 12%, however 57% remained above the target range. Reasons for non-compliance were evaluated, and protocol modifications were made accordingly. Between implementation of the CDSS in July 2008 and February 2010, two iterations of the protocol were evaluated. **Chapter 14** describes the impact of the protocol modifications on compliance and achievement of glycemic targets. The ICCU insulin protocol was modified in a stepwise manner. The first modification was made to manage insulin therapy in the case of decreasing glucose levels to prevent hypoglycaemic episodes and achieve a more stable normoglycemic state. The second modification consisted of a higher threshold for initiating insulin, wider glucose target ranges, and included instructions to regulate glucose around mealtimes. This stepwise modification of the ICCU insulin protocol resulted in an increase in protocol compliance with regard to timing of glucose measurements and better adherence to the advised insulin dosage. However, the percentage of patients achieving a mean glucose level <8mmol/l did not increase, illustrating the difficulty of regulating glucose in the ICCU

setting. Further work is needed to develop and validate better protocols for blood glucose regulation in the ICCU. A reliable, continuous glucose measurement system may be of great additional value in this setting.

In this thesis we describe three groups of studies reflecting the use of information technology to improve care in acute cardiology. First, pre-hospital ECG transmission and analysis in the triage of patients with suspected AMI and an in-hospital fast-track protocol to reduce time to reperfusion. Second, alarm management in the ICCU using an application to generate multimedia paging for faster, more adequate reaction to patient monitor alarms. Finally, a web-based, touchscreen CDSS to address hyperglycemia in the ICCU. Integration with the clinical workflow, thorough testing of the technology and meticulous, structured evaluation are key factors in successful implementation of a CDSS. Furthermore, long term commitment may be needed to achieve improvement in clinical outcomes.

The use of many different information systems within a single hospital is a challenge to implementing CDSS; any change in any of the systems requires adaptation of the CDSS. The CDSS described in the current thesis involve many, sometimes complex data coupling applications to extract and interpret information from different data sources. In many hospitals, information systems have 'evolved' over time and consist of many, non –or partially integrated databases. Initiatives to standardize medical data and communication protocols, along with hospital information systems that are fully integrated, so called "suites" can greatly facilitate the implementation and maintenance of CDSS.

SAMENVATTING EN DISCUSSIE

De kwaliteit van zorg in de acute cardiologie is de afgelopen decennia aanzienlijk verbeterd. Tegelijkertijd is ook het gebruik van informatietechnologie in de zorg en daarbuiten niet meer weg te denken. **Hoofdstuk 1** beschrijft het concept van klinische beslissingsondersteuning systemen, ook wel "clinical decision support systems" (CDSS) genoemd. Deze systemen maken een selectie uit de enorme hoeveelheid beschikbare data en presenteren relevante, patiëntspecifieke gegevens aan de zorgverlener met als doel het diagnostisch en therapeutisch pad te optimaliseren. Op afdelingen zoals de intensieve zorg worden veel beslissingen genomen op grond van data afkomstig van vele verschillende elektronische bronnen. Met name hier kan een CDSS van waarde zijn door informatie te vertalen naar adviezen voor een betere logistiek, diagnostiek en/of behandeling. Daarnaast kan een CDSS het naleven van richtlijnen en protocollen verbeteren, en inzicht geven in het gebruik. Echter, het succesvol implementeren van een CDSS is niet eenvoudig (1,2): het systeem moet goed aansluiten op de bestaande werkprocessen, en

geaccepteerd worden door de gebruikers. Evaluaties van het gebruik en klinische uitkomsten kunnen doorslaggevend zijn voor succesvolle implementatie van een CDSS.

Hoe sneller patiënten met een acuut myocardinfarct (AMI) worden behandeld, des de beter zijn de uitkomsten. Om de diagnose AMI vast te stellen, is een snelle en deskundige beoordeling van het electrocardiogram (ECG) van groot belang (3,4). In **hoofdstuk 2** is onderzocht in hoeverre ambulance verpleegkundigen een AMI kunnen detecteren. Ambulance verpleegkundigen identificeerden ECG's van 121 patiënten die zij als ST-elevatie AMI afgaven. Bij 49% van de patiënten werd de diagnose ook vastgesteld. Bij 60% van de ECG's zonder verdere abnormaliteiten stelden zij de juiste diagnose: in ECG's met bijkomende afwijkingen (waaronder een bundeltakblok, een oud infarct, of linkerventrikelhypertrofie) was dit 37%. Wanneer dezelfde ECG's door een cardioloog werden beoordeeld, werden 88% juist beoordeeld, ongeacht of er bijkomende afwijkingen zichtbaar waren. Deze resultaten benadrukken het belang van een gedegen ECG-training, met de nadruk op ECG's met bijkomende afwijkingen. Ook steunen deze resultaten initiatieven om ook pre-hospitale ECG's door een cardioloog te laten beoordelen.

Hoofdstuk 3 beschrijft het implementatietraject van een pre-hospitaal ECG-verzendsysteem in Guilford County, North Carolina. Hierbij worden ECGs vanuit de ambulance verzonden naar een centraal gelegen computer. Deze stuurt dan een elektronisch bericht naar de dienstdoende cardioloog. De cardioloog kan het ECG vervolgens inzien op een mobiel platform (zoals een PDA of "smartphone"), en contact op nemen met de ambulance om instructies te geven voor de behandeling. Een aantal zaken zijn van belang bij het implementatieproces. Ten eerste een goed georganiseerde ambulancedienst met verpleegkundigen die 12-afleidings ECG's kunnen afnemen. Tevens de beschikking over apparatuur om ECG's elektronisch te verzenden, en de faciliteiten om het systeem te kunnen testen, implementeren en onderhouden. Ook moeten de deelnemende ziekenhuizen 24 uur per dag, 7 dagen per week reperfusie therapie aanbieden. Ten slotte een onderzoekscentrum dat het implementatietraject overziet en het effect evalueert. Het implementatieproces is in te delen in een aantal fasen. In de eerste fase wordt de technologie gekozen en klinisch getest; behandel- en communicatieprotocollen worden vastgelegd en uitgangswaarden voor tijd tot reperfusiebehandeling worden verzameld. In fase twee worden de laatste testen van het systeem uitgevoerd, en eventuele aanpassingen gemaakt in de eerder opgestelde protocollen. In fase drie gaat het systeem "live", zodat cardiologen pre-hospitale behandelbeslissingen kunnen nemen, terwijl de kwaliteit en veiligheid van de patiëntenzorg bewaakt wordt door regelmatige evaluatie van de binnenkomenende data.

Hoofdstuk 4 beschrijft de ervaringen in Cabarrus County, North Carolina met een dergelijk systeem. Ambulance verpleegkundigen maken met de patiëntenmonitor een 12-afleidings ECG en verzenden deze elektronisch naar de spoedeisende hulp. Aldaar

wordt het ECG doorgestuurd naar de dienstdoende cardioloog die het ECG beoordeelt op een draagbare computer. De cardioloog beslist of de patiënt direct naar het cathlab kan komen of ter beoordeling naar spoedeisende hulp wordt gebracht. Vijf beschreven casus demonstreren het technisch functioneren, maar ook dat het met dit systeem mogelijk is binnen 35 minuten vanaf aankomst in het ziekenhuis reperfusie te bereiken. Ook wordt de opzet van de TIME-NE trial (5) beschreven, waar het effect van een pre-hospitaal ECG-verzendsysteem op de tijd tot reperfusie is onderzocht. Patiënten met een elektronisch verstuurd ECG hadden de kortste tijd tot reperfusie (50 [80 – 132] minuten); patiënten waarbij het versturen mislukte hadden een langere tijd tot reperfusie (78 [64 – 109]) minuten. Echter, in de controle groep (vóór implementatie van het systeem) was de tijd tot reperfusie het langst: 101 (80 – 132) minuten. Onvoldoende dekking door draadloze netwerken was een belangrijke reden voor het niet ontvangen van het ECG door de cardioloog. Ook verliep het versturen vanuit de ambulance soms problematisch, maar verbeterde na uitgebreidere instructies aan de verpleegkundigen.

Een andere benadering, door met een geautomatiseerd algoritme ECG's in de ambulance te beoordelen, is in Rotterdam en omstreken reeds 20 jaar in gebruik (6), en wordt derhalve in dit proefschrift niet nader beschreven. Een ECG-verzendsysteem met beoordeling door een cardioloog heeft als voordelen een optimale ECG-beoordeling en de mogelijkheid voor te bereiden op aankomst van de patiënt. De betrouwbaarheid van het systeem is echter beperkt door de dekking van mobiele en draadloze netwerken. Beoordeling van het ECG door ambulanceverpleegkundigen is minder afhankelijk van technologie, maar valt of staat bij een gedegen ECG training en heeft een lagere specificiteit bij ECG's met bijkomende afwijkingen. Een gecombineerde oplossing, waarbij alleen moeilijk te interpreteren ECG's worden verzonden, kan een uitkomst bieden.

Niet alleen het pre-hospitale traject, maar ook de tijd vanaf aankomst in het ziekenhuis tot reperfusie bij AMI patiënten kan verkort worden. **Hoofdstuk 5** beschrijft drie interventies die tot een tijdswinst van gemiddeld 39 minuten opleverden voor het bereiken van reperfusie. De eerste interventie was een zogenaamd "hart-alarm" als aankondiging voor een AMI patiënt. Het hart-alarm is een bericht dat elektronisch wordt verzonden naar de piepers van de dienstdoende cardioloog, de coördinator van het cathlab, de dienstdoende laboranten (ECG, laboratorium en röntgen) en de baliemedewerker van de spoedeisende hulp. Als tweede werd de "deur tot reperfusie" tijd teruggekoppeld aan de interventiecardiologen. Ieder kwartaal ontvingen zij de eigen tijden en de gemiddelde tijd van alle cardiologen. Als laatste werd de bezetting van het cathlab uitgebreid tot 24 uur per dag, 7 dagen per week met een continue aanwezig team (hiervoor was er een team aanwezig van maandag tot en met vrijdag van 7.00 tot 19.00, en hierbuiten oproepbaar). Deze interventies zijn voorbeelden van relatief eenvoudige maatregelen die de door een verkorting van de tijd tot reperfusie de kwaliteit van zorg bij AMI patiënten kunnen verbeteren.

Ernstig zieke patiënten op een intensieve zorgafdeling worden daar aangesloten op

meerdere patiëntbewakingsapparaten, die een alarm afgeven bij een afwijkende meetwaarde. Echter, verreweg de meeste alarmen zijn "onschuldig" en duiden niet op een levensbedreigende toestand. **Hoofdstuk 6** beschrijft 34.827 alarmen op de intensieve hartzorgafdeling (ICCU). De alarmfrequentie was gemiddeld 2,2 per patiënt per uur, maar varieerde sterk. De meeste alarmen kwamen overdag en bij de verzorgingsmomenten voor. Bij verhoogde activiteit zijn er ook meer bewegingsartefacten die, net als bij een levensbedreigende situatie, meerdere afwijkende meetwaarden kunnen veroorzaken. Het verzamelen van alarmen afkomstig van patiëntbewakingsapparatuur van meerdere producenten is een uitdaging op zich. Vanaf 1997 zijn er initiatieven om de onderlinge elektronische informatieuitwisseling in de zorg te verbeteren (7). In 2008 werd het "alarm communication profile" (8) voorgesteld om de uitwisseling van alarmberichten mogelijk te maken. **Hoofdstuk 7** beschrijft de "intelligent Patient Universal Tele-alarm" (i-PUT), een open-source "toolkit" waarmee dit profiel in het Thoraxcentrum van het Erasmus MC is geïmplementeerd. Deze toolkit bevat verschillende componenten. De voornaamste is de alarmbeheerder, die alarmberichten ontvangt, opslaat en verstuurt via verschillende, configureerbare kanalen (e-mail, instant messaging, SMS en "pager" protocollen). Een tweede component laat de gebruiker zoekopdrachten uitvoeren in de alarmdatabase om bijvoorbeeld inzicht te krijgen in de frequentie en verdeling van alarmen (zoals beschreven in **hoofdstuk 6**).

I-PUT kan ook gebruikt worden om laboratoriumuitslagen, adviezen van een CDSS en andere informatie door te sturen naar de zorgverlener, wat mogelijkheden biedt om de kwaliteit en efficiëntie van de zorg te verbeteren. Een configureerbare web-interface (**Hoofdstuk 8**) kan hiervoor gebruikt worden. Hiermee kunnen alarmen op op patiënt – en afdelingsniveau weergegeven worden. Bij het selecteren van een alarmbericht, worden de vitale gegevens ten tijde van het alarm weergegeven. Zo kan de zorgverlener een overwogen beslissing nemen tot actie. De web-interface is toegankelijk via verschillende "smartphone" systemen waaronder i-Phone, Android, Windows Mobile en Blackberry.

De mogelijkheden van een alarm beheersysteem, zoals i-PUT, zijn groot, echter bij implementatie is het van belang rekening te houden met mogelijke effecten op de patiëntenzorg. Zorgverleners zitten namelijk niet te wachten op extra alarmen op een pieper, mobiele telefoon en/of PDA; de alarmen moeten alleen worden doorgegeven indien dit de kwaliteit van patiëntenzorg positief beïnvloedt. Een toename van vals-positieve alarmen kan leiden tot een tragere reactie op, of zelfs het geheel negeren van "echte" alarmen. Eerst moet de frequentie van alarmen worden teruggebracht. Dit kan bijvoorbeeld door "over"bewaking van patiënten te voorkomen en alarmgrenzen goed in te stellen. Ook het gebruik van mobiele apparaten om sneller en adequater te kunnen reageren op klinische alarmen lijkt veelbelovend, maar moet eerst klinisch getest worden; vervolgens kan het effect van een alarmbeheersysteem op de kwaliteit en efficiëntie van de patiëntenzorg worden onderzocht.

Patiënten met een AMI en diabetes mellitus, maar ook patiënten met verhoogde glucose zonder vastgestelde diabetes, hebben een slechtere prognose. **Hoofdstuk 9** geeft een overzicht van de voornaamste onderzoeken met IGL. Hieruit blijkt dat IGL met als streven normale glucosewaarden de overleving verbetert en het optreden van complicaties vermindert (10). Echter, een goede glucoseregulatie is moeilijk te bereiken en de insulinebehandeling kan leiden tot een snelle daling glucosewaarden met als gevolg hypoglycemie (11,12). Ook is een andere behandeling, het systematisch toedienen van een glucose-insuline-kalium infuus (GIK) bij AMI patiënten voorgesteld (9). De eerste onderzoeken lieten hierbij minder ritmestoornissen en een verbeterde overleving lieten zien. Echter in recentere en grotere onderzoeken had GIK geen gunstige effecten en wordt het niet meer toegepast.

Hoofdstuk 10 beschrijft de prognostische waarde van hyperglycemie bij 1713 patiënten op de ICCU. Een stijging van de glucose bij opname van 1 mmol/l (boven de 9 mmol/l) gaf een 10% (95% CI 7% - 13%) hoger risico op sterfte. Bij 893 van de patiënten waren er 3 of meer glucosemetingen en werd de gemiddelde glucoseconcentratie tijdens opname berekend: een stijging van de gemiddelde glucose van 1 mmol/l (boven de 8 mmol/l) gaf een 11% (95% CI 3% - 20%) hoger risico op sterfte. Regressie analyse werd verricht om rekening te houden met ernst van ziekte, en andere risicofactoren zoals leeftijd, geslacht, diabetes, doorgemaakte hart/vaatziekten en nieraandoeningen.

Om de glucosewaarden te verlagen gebruiken veel ziekenhuizen insulineprotocollen. Het goed naleven van een insuline protocol op papier kan lastig zijn. Op de ICCU werden slechts 37% van de glucosemetingen op tijd afgenomen; ook de dosering van insuline werd slechts bij de helft van de metingen nageleefd. Deze bevindingen (**Hoofdstuk 11**) vormden de aanleiding om een CDSS voor glucoseregulatie te ontwikkelen. Eerst werden obstakels voor het naleven van het protocol geïdentificeerd. Ten eerste werden zorgverleners niet automatisch op de hoogte gebracht van een nieuwe glucosewaarde. Ook was het insuline protocol niet goed zichtbaar en ten slotte waren zorgverleners bezorgd dat een strikte naleving van het protocol tot hypoglycemie zou leiden. Deze bevindingen werden, aangevuld met input van multidisciplinair overleg, gebruikt om een web-based CDSS voor glucoseregulatie te ontwikkelen. Dit CDSS is beschreven in **hoofdstuk 12** bestaat uit een computer met aanraakbaar scherm. Op het scherm zijn de ICCU bedden afgebeeld met daarop de gegevens van de opgenomen patiënten, glucosewaarden en insulinepompstanden. Bij een nieuwe glucosemeting verschijnt er een "pop-up" bij de betreffende patiënt. Deze pop-up bevat de glucosewaarde, de tijd van de meting, een advies voor de insulinepompstand en de tijd van de volgende meting. Het CDSS slaat alle data op, en is uitbreidbaar met een beslisregel beheersysteem, waarmee beslisregels met een grafische interface aangepast kunnen worden (en dus ook door de zorgverleners zelf gewijzigd kunnen worden).

Hoofdstuk 13 beschrijft 425 patiënten voor implementatie van het CDSS, en 243 erna.

Implementatie van het CDSS voor glucoseregulatie leidde tot een verbeterde naleving van het insuline protocol van 12%, zowel met betrekking tot het op tijd meten van de glucose als het doseren van insuline. Ook steeg het aandeel patiënten met een “goede” gemiddelde glucose (4,5 - 7 mmol/l) met 12%. Echter, bij 57% van de patiënten bleef de gemiddelde glucose te hoog.

De redenen voor het niet naleven van het protocol werden geïnventariseerd en gebruikt om het protocol aan te passen. Vanaf de CDSS implementatie in juli 2010 en februari 2010 werden twee iteraties van het protocol doorgevoerd. **Hoofdstuk 14** beschrijft de impact van de aanpassingen op het naleven van het protocol en op het bereiken van streefwaarden voor glucose. De eerste aanpassing werd gedaan om insuline beter te doseren bij dalende glucosewaarden zodat glucosewaarden sneller stabiliseren en hypoglycemie niet optreedt. De tweede aanpassing betrof het toevoegen van instructies voor het toedienen van insuline rondom de maaltijden en een verruiming van de streefwaarden voor glucose. Deze stapsgewijze aanpassing van het insulineprotocol leidde tot een verbeterde naleving. Echter, het aandeel patiënten met een gemiddelde glucose binnen de streefwaarde (<8 mmol/l) nam niet toe, en illustreert de complexiteit van glucoseregulatie op de ICCU. Onderzoek naar verdere protocolaanpassingen, eventueel gecombineerd met een betrouwbaar, continue meetsysteem voor glucose is nodig om een goede glucoseregulatie op de ICCU te bereiken.

Dit proefschrift beschrijft drie thema's waarin informatietechnologie wordt toegepast om de kwaliteit van zorg in de acute cardiologie te verbeteren. Ten eerste het verzenden en beoordelen van ECG's vanuit de ambulance om de behandelingstijd bij AMI patiënten te verkorten. Ook was een pakket aan maatregelen waaronder een “hart-alarm” effectief om het traject binnen het ziekenhuis te verkorten. Het tweede thema gaat in op het beheren van alarmen van patiëntbewakingsapparatuur. Hierbij kan een alarmbeheersysteem kan “slimmere” alarmberichten genereren om zorgverleners sneller en adequater te laten reageren op alarmen.

Het laatste thema beschrijft het implementeren van een CDSS aan de hand van een insulineprotocol voor patiënten op de ICCU. Een succesvolle implementatie vereist een goede integratie met de bestaande zorgprocessen, een hoge technische betrouwbaarheid en een zorgvuldige, gestructureerde evaluatie. Tevens kunnen verbeteringen van klinische uitkomsten pas na langere tijd zichtbaar worden.

In de meeste ziekenhuizen is het ziekenhuisinformatiesysteem over vele jaren geëvolueerd tot een verzameling (gedeeltelijk) geïntegreerde systemen en databases. Dit maakt het implementeren en onderhouden van een CDSS een ingewikkelde zaak; een aanpassing in één van de systemen vergt namelijk ook een aanpassing van het CDSS. De projecten beschreven in dit proefschrift maken gebruik van vele, soms zeer complexe koppelingen om data uit de verschillende systemen te halen. Het standaardiseren van invoer, opslag en

uitwisseling van medische informatie, maar ook de opkomst van volledig geïntegreerde ziekenhuisinformatiesystemen (zogenaamde “suites”) kunnen de implementatie en het onderhoud van een CDSS aanzienlijk faciliteren.

REFERENCES / REFERENTIES

1. Ash JS, Berg M, Coiera E. Some unintended consequences of information technology in health care: the nature of patient care information system-related errors. *J Am Med Inform Assoc.* 2004 Apr;11(2):104-112.
2. Han YY, Carcillo JA, Venkataraman ST, Clark RSB, Watson RS, Nguyen TC, et al. Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system. *Pediatrics.* 2005 Dec;116(6):1506-12.
3. Bouten MJ, Simoons ML, Hartman JA, van Miltenburg AJ, van der Does E, Pool J. Prehospital thrombolysis with alteplase (rt-PA) in acute myocardial infarction. *Eur. Heart J.* 1992 Jul;13(7):925-931.
4. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet.* 1996 Sep 21;348(9030):771-775.
5. Adams GL, Campbell PT, Adams JM, Strauss DG, Wall K, Patterson J, et al. Effectiveness of prehospital wireless transmission of electrocardiograms to a cardiologist via hand-held device for patients with acute myocardial infarction (from the Timely Intervention in Myocardial Emergency, NorthEast Experience [TIME-NE]). *Am. J. Cardiol.* 2006 Nov 1;98(9):1160-1164.
6. Grijseels EW, Deckers JW, Hoes AW, Boersma E, Hartman JA, van der Does E, et al. Implementation of a pre-hospital decision rule in general practice. Triage of patients with suspected myocardial infarction. *Eur Heart J.* 1996 Jan;17(1):89-95.
7. Integrating the Healthcare Enterprise: IHE.net Home. Available from: <http://www.ihe.net/>.
8. Integrating the Healthcare Enterprise: PCD Profile Alarm Communication Management Wiki. Available from: <http://wiki.ihe.net/index.php?title=ACM>.
9. SODI-PALLARES D, BISTENI A, MEDRANO GA, TESTELLI MR, DE MICHELI A. The polarizing treatment of acute myocardial infarction. Possibility of its use in other cardiovascular conditions. *Dis Chest.* 1963 Apr;43:424-432.
10. Malmberg K, Rydén L, Efendic S, Herlitz J, Nicol P, Waldenström A, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J. Am. Coll. Cardiol.* 1995 Jul;26(1):57-65.
11. Malmberg K, Rydén L, Wedel H, Birkeland K, Bootsma A, Dickstein K, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur. Heart J.* 2005 Apr;26(7):650-661.
12. The NICE-SUGAR Study Investigators. Intensive versus Conventional Glucose Control in Critically Ill Patients. *N Engl J Med.* 2009 Mar 26;360(13):1283-1297.

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PHD PORTFOLIO SUMMARY

Summary of PhD training and teaching activities

Name PhD student: Jonathan Lipton
 Erasmus MC Department: Cardiology
 Research School: COEUR

PhD period: 1/1/2005 – 30/3/2010
 Promotor: M. Simoons

Activities	Year	Workload (Hours/ECTS)
Courses		
- Study design (CC01)	2008-2010	4.2
- Classical methods for data analysis (CC02)		5.7
- Principles of research in medicine (ESP01)		0.7
- Methods of public health research (ESP11)		0.7
- Health economics (ESP25)		0.7
- Introduction to public health (ESP41)		0.7
- Methods of health services research (ESP42)		0.7
- Primary and Secondary prevention research (ESP45)		0.7
- Advanced topics in decision-making in medicine (EWP02)		1.9
- Diagnostics research (EWP05)		0.9
- Prognosis research (EWP16)		0.9
- Knowledge Representation in Medicine (EXT16)		6
In-depth courses		
- Molecular Medicine, SNP's and human disease	2005-2010	2
- COEUR, Molecular biology in cardiovascular research		1.5
- COEUR, pathophysiology of ischemic heart disease		1.5
- COEUR, cardiovascular pharmacology		1.5
- COEUR, vascular clinical epidemiology		2
- Netherlands Intensive Care Association, Fundamental Critical Care Support		1.5
- Advanced Cardiac Life Support (annual)		2.7
Presentations		
- NVVC	2005	2
- Netherland Heart Association	2005	1
- European Society of Cardiology	2005-2009	2
- Computers in Cardiology	2005-2009	4

Acute	Activities	Year	Workload (Hours/ECTS)
	Conferences		
	- European Society of Cardiology	2005-2009	1.8
	- Computers in Cardiology	2005-2009	2.7
	- NVVC	2005-2010	3
	Seminars and workshops		
	- STAFF research meetings	2005-2010	6
	- Scientific Summer School	2008	2
	Didactic skills		
	- Scientific Summer School "Teach the Teacher"	2009	2
	Teaching		
	- Junior Med School	2008, 2009	2
	- Literature review project	2009	2
	- Masters thesis	2010	1
		Total	68

CURRICULUM VITAE

The author of this thesis was born on May 25th 1978 in Evansville, Indiana, USA. He graduated secondary school in 1996 at the Stedelijk Gymnasium Haarlem. From 1996 - 2003 he studied Medicine at the Leiden University. During this period he did an elective research project at Duke University, North Carolina and an elective clinical rotation at Queens Elizabeth Hospital in Malawi. After graduation, he worked for one year as a clinical research fellow in West Virginia in a collaborative project with Duke University. In 2005 he started a combined PhD and residency program in Cardiology at the Erasmus Medical Center in Rotterdam (Research supervisor: Prof.dr. M.L. Simoons; clinical supervisor: dr. F.J. ten Cate). The cardiology training includes a two year internal medicine residency (From 2006 - 2008 at the St. Franciscus Gasthuis in Rotterdam, supervisor dr. A. Rietveld) and a six month residency at a peripheral medical center (2010 at the Albert Schweitzer Hospital in Dordrecht, supervisor dr. M.J.M. Kofflard). His other interests include travelling, mountain climbing, cycling and running.

*An up-to-date curriculum vitae and list of publications is available at:
www.acutecardiology.com/cv*

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