Understanding Effective and Timely Administration of Loop Diuretics for the Treatment of Acute Heart Failure: A Quality Improvement Intervention and Evaluation

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science

Institute of Medical Science
University of Toronto

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2016

ABSTRACT

Objectives: Intravenous administration of loop diuretics is a cornerstone of therapy for acute heart failure. We developed and evaluated the MSH La6 Protocol, a tool to standardize practices for administration, monitoring and dose adjustment of IV furosemide over a 48-hour period and delegated autonomy to the nurse at the point of care.

Results: There were no serious adverse events and no deaths. Between the pre- and post-implementation period, a significant and stable improvement was observed in the monitoring of patients receiving IV furosemide. A significantly larger proportion of patients treated using the La6 Protocol had a furosemide dose increase in the 24-48 hour block versus patients treated with usual care.

Conclusions: An intervention that resulted in improved adherence to practices for monitoring was also associated with the observation that furosemide dosage was up titrated more frequently early during hospital admission.
Acknowledgements

First and foremost, I would like to express my sincere gratitude to my supervisor, Dr. Susanna Mak. Without her innovative thinking and tremendous dedication, this project would not have been possible. I would also like to thank Dr. Mak for her continual mentorship and support in my learning. Her devotion to teaching is unparalleled and valued by all the students within our group.

I am grateful to my supervisory committee Dr. Chaim Bell and Dr. Douglas Lee for their support and guidance throughout this project. I would like to sincerely thank Dr. Andrew Wyllie for his valuable input and encouragement every step of the way. I would also like to acknowledge Dr. Gary Newton for his insight and advice in developing this work.

I would like to thank all of the nursing staff and nursing administration on the cardiology and medicine wards at Mount Sinai Hospital for participating in this practice change. I am also thankful for the support I received in this initiative from the cardiologists at our institution.

I will never forget the never-ending support I received from the students in our group – Sam Esfandiari, Daniela Malta, Kelsey McLaughlin, and Steve Wright. Their help and friendship has meant the world.

This accomplishment would not have been possible without the support of my loving husband and family. The gratitude I feel to my parents is immeasurable and all of my successes are possible because of their unwavering love, strength and support. I dedicate this work to them.
Contributions

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Abbreviated Terms

ACB – aortocoronary bypass
ACE - angiotensin converting enzyme
ADHERE - Acute Decompensated Heart Failure National Registry
ADHF – acute decompensated heart failure
AHF – acute heart failure
AKI – acute kidney injury
ALP - alkaline phosphatase
ALT - alanine aminotransferase
ARB - angiotensin receptor blockers
AST - aspartate aminotransferase
BNP - brain natriuretic peptide
BP – blood pressure
BUN - blood urea nitrogen
Ca\(^{2+}\) - calcium
CARRESS-HF - The Cardiorenal Rescue Study in Acute Decompensated Heart Failure
CTU – clinical teaching unit
DIA - diastolic
DOSE - Diuretic Optimization Strategies Evaluation
ED – emergency department
EFFECT - Enhanced Feedback for Effective Cardiac Treatment
eGFR – estimated glomerular filtration rate
EPR – electronic patient record
ESRD – end stage renal disease
Hb – hemoglobin
HF – heart failure
HFpEF – heart failure with preserved ejection fraction
HFrEF – heart failure with reduced ejection fraction
Ht – hematocrit
HTN – hypertension
ICU – intensive care unit
INR – international normalized ratio
IOM – institute of medicine
IPC – interprofessional collaboration
IQR – interquartile range
IV - intravenous
JVP – jugular venous pressure
K - potassium
LOS – length of stay
MI – myocardial infarction
MRI – magnetic resonance imaging
MRP – most responsible physician
MSH – Mount Sinai Hospital
Na⁺ - sodium
NICE - National Institute for Health and Clinical Excellence Guidance

NIH – National Institutes of Health

Nomo-SDC – Nomogram for Stepped Diuretic Care

NT-proBNP - N-terminal pro b-type natriuretic peptide

NYHA – New York Heart Association

PCI – percutaneous coronary intervention

PND – paroxysmal nocturnal dyspnea

PO – per os

PPOS – Physician Preprinted Order Set

QI – quality improvement

RCT – randomized control trial

RIFLE - Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease

RN – registered nurse

SBP – systolic blood pressure

SCr – serum creatinine

SD – standard deviation

SPSS - Statistical Package for the Social Sciences

SYS - systolic

UK-Heart - United Kingdom Heart Failure Evaluation and Assessment of Risk Trial
1 Heart Failure

1.1 Heart Failure: General Overview

The purpose of this section is to provide a general summary and is not intended as an exhaustive review. Heart Failure (HF) is a complex clinical syndrome that arises from a variety of cardiac diseases and results in progressive impairment of systemic perfusion that is insufficient to keep up with metabolic demands (Cowie et al., 1997). Although incidence has steadily decreased over the past couple of decades, increasing size of the aging population has resulted in a rise in prevalence of heart failure over time (W. H. Barker, Mullooly, & Getchell, 2006; Braunwald, 1997, 2013; Cowie et al., 1997; Heidenreich et al., 2013; Ho, Pinsky, Kannel, & Levy, 1993; Levy et al., 2002; Mosterd & Hoes, 2007; Yeung et al., 2012). The lifetime risk of HF is higher in women (1 in 6) versus men (1 in 9) at 40 years old; risk is also doubled in those with blood pressure (BP) >160/90 mmHg versus those with BP <140/90 mmHg (Lloyd-Jones et al., 2002). Two commonly utilized classification systems of heart failure summarize the symptomatic state of the patient as well as the severity of disease. The first was developed by the New York Heart Association (NYHA) and divides heart failure severity into 4 classes based on the functional limitations of the patient.

- Class I – Heart disease present; no limitation of physical activity.
- Class II – Heart disease present; limitation of physical activity present during routine and regular activity.
- Class III – Heart disease present; limitation of physical activity present with less than routine physical activity. No symptoms at rest.
- Class IV – Heart disease present; symptoms present with any physical activity and at rest.
The second classification system divides heart failure based on its stage of development and was conceived by the American Heart Association. It identifies the following 4 stages of heart failure (Yancy et al., 2013):

- **Stage A** – High risk of heart failure; absence of structural heart disease or symptoms of HF.
- **Stage B** – Presence of structural heart disease; absence of signs or symptoms of HF.
- **Stage C** – Presence of structural heart disease; presence of prior or current symptoms of HF.
- **Stage D** – Refractory HF requiring specialized care.

Both classification systems are valuable in establishing the presence and severity of heart failure and therefore guiding therapeutic strategies.

Heart failure can be caused by a vast variety of illnesses affecting every layer of cardiac tissue (pericardium, myocardium, endocardium) as well as the vasculature and valvular apparatus (Cowie et al., 1997). e. The syndrome of heart failure related to left ventricular chamber abnormalities is divided into patients that clearly demonstrate reduction of the left ventricular ejection fraction (<40 percent) and is known as heart failure with reduced ejection fraction (HFrEF), or previously, systolic heart failure. Another group of patients with heart failure are presumed to have abnormalities of diastolic performance because the left ventricular ejection fraction is reasonably preserved (>40 percent) and this is known as heart failure with preserved ejection fraction or HFpEF. The older term for this subtype is diastolic heart failure. Appropriate diagnosis of HFrEF or HFpEF is crucial for proper management of chronic heart failure. The prevalence of cardiac diseases that lead to the development of heart failure has also changed over the past few decades due to changes in socio-economic status as well as
improvements in preventative strategies, diagnosis and therapeutics (Cowie et al., 1997; Kannel, Ho, & Thom, 1994; Mozaffarian et al., 2016). The age-adjusted incidence and prevalence of conditions such as hypertension and ischemic heart disease that contribute to the development of heart failure are decreasing (He et al., 2001; Lloyd-Jones et al., 2002). However, these gains have been offset by the increasing incidence of diabetes mellitus, a significant concern as a cause of heart failure (Owan et al., 2006). In Canada, the self-reported prevalence of heart disease (including myocardial infarction, angina and heart failure) is 4.2% in women and 5.3% in men ("Tracking Heart Disease and Stroke in Canada," 2009).

The diagnosis of symptomatic (Stage C and D) heart failure is based on a multifaceted clinical assessment, composed of a carefully taken medical history of the patient as well as a thorough physical examination as there is no single conclusive diagnostic test available. There are 2 helpful diagnostic investigations that are commonly used to aid in the proper diagnosis of heart failure for a patient presenting with suggestive symptoms. Serum B-type natriuretic peptide (BNP) is secreted primarily by the ventricular myocyte in response to increased wall stress. It is secreted as a pro-peptide and cleaved into the active peptide (BNP) and the N-terminal end (NT-pro-BNP), both fragments can be measured in serum using commercially available assays. In the setting of increased ventricular wall stress, both BNP and NT-pro-BNP will be elevated in the blood. This marker is very helpful in establishing diagnosis when used in conjunction with a careful history taking and physical examination. Current guidelines also present evidence showing decreased mortality when BNP guided therapy is used to treat heart failure (Kelder et al., 2011; Moe et al., 2015; Yancy et al., 2013). A second useful diagnostic tool is transthoracic 2-dimensional echocardiography combined with a Doppler ultrasound examination (Heart Failure Society of et al., 2010; McKelvie et al., 2013; Yancy et al., 2013). This noninvasive
diagnostic assessment examines hemodynamics and cardiac function in patients with signs and symptoms of heart failure. A complete echocardiographic examination evaluates chamber sizes, ventricular function and wall motion abnormalities and can often yield clues as to the etiology of heart failure (Cheitlin et al., 2003). Other cardiac diagnostic tools include an electrocardiogram, a chest x-ray, exercise stress testing, and advanced imaging such as magnetic resonance imaging (MRI) (Pennell et al., 2004) and cardiac catheterization (Yancy et al., 2013). More specifically, these tools are valuable in establishing the etiology of heart failure.

There are cardinal clinical signs and symptoms that suggest the diagnosis of heart failure. They can be divided into those that reflect insufficient cardiac output and those that reflect fluid congestion in various tissues. In cardiac conditions predisposing to heart failure, inadequate increases in cardiac output occur during periods of increased metabolic demand such as exertion and patients experience weakness and fatigue. The decrease in cardiac output, in turn, causes neurohumoral activation and impaired intrarenal hemodynamics leading to worsening renal function, and in some cases leading to the development of the cardiorenal syndrome (Liu, 2008). These complex pathophysiological processes then lead to excess fluid accumulation in different tissues (Braunwald, 2013; Liu, 2008). Symptoms associated with fluid accumulation are dependent on the affected organ and include dyspnea and paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, right lower quadrant tenderness from hepatic congestion, and ascites (Maisel et al., 2002). There may be many more signs and symptoms present based on the underlying heart disease.

There are diagnostic criteria available to assist in the proper diagnosis of heart failure. Several criteria have been validated, including the Framingham, Boston and Duke scales. The
most widely used of the three is the modified Framingham clinical criteria for the diagnosis of heart failure, which has excellent sensitivity and specificity and includes the following:
Table 1. Framingham Clinical Criteria for Diagnosis of Heart Failure

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthopnea</td>
<td>Weight loss $\geq 4.5$ kg in five days</td>
</tr>
<tr>
<td>Pulmonary rales</td>
<td>Tachycardia (heart rate $\geq 120$ beats/min)</td>
</tr>
<tr>
<td>Cardiomegaly on chest x-ray</td>
<td>Pleural effusion</td>
</tr>
<tr>
<td>Pulmonary edema on chest x-ray</td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
<td>Dyspnea on ordinary exertion</td>
</tr>
<tr>
<td>Elevated jugular venous pressure</td>
<td>Nocturnal cough</td>
</tr>
<tr>
<td>Third heart sound</td>
<td>Bilateral leg edema</td>
</tr>
<tr>
<td>Weight loss $\geq 4.5$ kg in five days in response to treatment of presumed heart failure*</td>
<td></td>
</tr>
</tbody>
</table>
The diagnosis of heart failure based on the Framingham criteria requires 2 major or 1 major and 2 minor criteria.

Management of chronic Stage C and D heart failure encompasses a few important components – education and control of risk factors, including coronary artery disease, cigarette smoking, hypertension, obesity, diabetes and valvular heart disease (Gopal et al., 2012; He et al., 2001, 2002; Nkomo et al., 2006) as well as lifestyle modification (Djousse, Driver, & Gaziano, 2009), and pharmacological therapy. The goals of therapy in stage C and D are aimed at improving symptoms, reducing or slowing down the structural damage of the heart as well as reducing mortality. Several clinical trials have shown benefit on reducing mortality with the appropriate use of angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), hydralazine and nitrates, aldosterone antagonists and beta-blockers (McKelvie et al., 2013; Pitt et al., 1999). Evidence for treatment of HFpEF is more limited.

In advanced heart failure, after guideline-directed medical therapy with the above-mentioned drugs has been used, certain strategies exist to control ongoing symptoms of heart failure, particularly those related to congestion. There are observational studies that show benefit with salt restriction (Arcand et al., 2011; Bennett et al., 1998; He et al., 2002; Lennie et al., 2011; Son, Lee, & Song, 2011; Tsuyuki et al., 2001) (2grams/day or 3grams/day based on source of recommendation (Heart Failure Society of et al., 2010; McMurray et al., 2012; Yancy et al., 2013)) and fluid restriction in refractory heart failure. Despite control of chronic symptoms of heart failure and optimal medical therapy, patients still experience episodes during which symptoms worsen. The next section describes the clinical entity of acute heart failure.

There are many factors that determine the prognosis of patients diagnosed with heart failure. The etiology, patients’ demographics, management strategy, patient compliance, and
hospitalizations are all important predictors. Although prevalence of heart failure has increased over the years, in part due to increasing aging population and improved methods of heart failure management, mortality reduction has steadily improved, as evidenced by numerous studies (Brophy, 1992; Cowie et al., 1997).

1.2 Acute Heart Failure (AHF)

Although heart failure is considered a chronic and progressive condition, its course is punctuated by episodes of acute worsening of symptoms due to a number of disease-specific as well as external factors requiring specific therapy. The most current guidelines on management have defined these episodes as ‘acute heart failure’ (McKelvie et al., 2013), with some still referring to the older term of ‘acute decompensated heart failure’ (Gupta, Ghimire, & Hage, 2014; Heart Failure Society of et al., 2010; McKelvie et al., 2013). Acute heart failure presents as an exacerbation of symptoms usually controlled with medication and lifestyle modification, with the most common constellation of symptoms referred to as congestion, further discussed in Section 1.2.1.

Acute heart failure is responsible for the majority of unplanned hospitalization for patients either suffering from chronic heart failure, or as the initial presentation of heart failure. The Canadian Institute for Health Information considers heart failure an ambulatory care sensitive condition, such that appropriate ambulatory care may reduce the need for admission to hospital. The hospitalization rate for heart failure is expressed as age-standardized acute care hospitalization rate per 100,000 population younger than age 75, (Health Indicators 2013: Definitions, Data Sources and Rationale, May 2013, 2013) calculated as the total number of acute care hospitalizations for ambulatory care sensitive conditions younger than age 75 / total mid-year population younger than age 75 × 100,000 (age adjusted). The age adjusted admission
rate to hospital with the primary diagnosis of heart failure has steadily declined around the world in the last 20 years (Chen, Normand, Wang, & Krumholz, 2011; Jhund et al., 2009; Schaufelberger, Swedberg, Koster, Rosen, & Rosengren, 2004; Tu, Nardi, et al., 2009). In Canada hospitalization rate fell 27.2% between 1994 and 2004 (Tu, Nardi, et al., 2009). It is hypothesized that the decline in incidence of heart failure contributed to this change in hospitalization rate. Age-adjusted mortality has also declined (Roger et al., 2004). However, the combination of improved survival and the increasing size of the elderly population is such that the total burden of hospitalization remains very high (Fang, Mensah, Croft, & Keenan, 2008; Lee et al., 2004).

Despite the improvement, several studies have shown that mortality and rehospitalization rates remain high following a hospitalization (Krumholz et al., 1997; Roger et al., 2004; Solomon et al., 2007). The need for hospitalization remains an important determinant of short-term prognosis in heart failure patients. Mortality was found to be highest within one month of discharge for heart failure (Solomon et al., 2007).

1.2.1 Congestion in the Setting of Acute Heart Failure

Congestion refers to the accumulation of fluid in the body that occurs as a consequence of several compensatory mechanisms the body utilizes in response to the decreased cardiac output in heart failure. The compensatory neurohormonal adaptations initially work to maintain systemic pressure and perfusion of vital organs as well as restore normal cardiac output. However, with time, these adaptations lead to a constellation of negative consequences that, when combined, present as clinical signs and symptoms of congestion (Francis, Goldsmith, Levine, Olivari, & Cohn, 1984). One of the compensatory neurohormonal adaptations is the activation of the renin-angiotensin-aldosterone system. Within this mechanism, Angiotensin II
causes sodium reabsorption, which in turn causes an expansion of extracellular fluid and an increase in diastolic pressures. Although initially acting as a compensatory mechanism meant to restore cardiac output, with time the increased venous return causes an elevation in capillary pressures and the development of pulmonary and peripheral congestion. Fluid accumulation in the lungs results in symptoms of dyspnea, fatigue, paroxysmal nocturnal dyspnea (PND) and orthopnea. Peripheral venous congestion manifests as symptoms of peripheral edema, extending from the lower limbs all the way up to the abdominal cavity, as well as an elevated jugular venous pressure, ascites and poor appetite.

Several large databases have recorded high quality data on patients admitted with acute heart failure and extensively describe multiple clinical characteristics of patients admitted to hospital. The Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study includes Canada’s largest databases of acute heart failure patients from 86 hospital corporations in Ontario. The study included 9293 patients admitted to hospital with AHF. The results revealed the patients mean age to be 77 years old, with 51% being female (Tu, Donovan, et al., 2009). Similar demographics were demonstrated in the Acute Decompensated Heart Failure National Registry (ADHERE), which collected data in patients hospitalized with the primary diagnosis of acute heart failure in 263 hospitals in the United States. The study included 105 388 patients and showed the proportion of patients displaying the above-mentioned clinical symptoms of congestion. Symptoms consistent with pulmonary edema were present in 88% of patients, and specifically included fatigue in 30% of patients, and dyspnea in 91% of patients. Peripheral edema on examination was found in 66% of patients (W. F. t. Peacock et al., 2008).

1.3 Treatment of Acute Heart Failure
The evidence base for the treatment of chronic heart failure in the ambulatory care setting is well developed. However, a substantial portion of heart failure care is directed at acute heart failure, these episodes of clinical worsening that are unpredictable and frequently require urgent or emergent care, usually in a hospital based setting and often require admission. The approach to management of AHF is similar for both patients with HFrEF or HFpEF. Patients seen in the emergency department in acute distress from symptoms of AHF, such as acute pulmonary edema leading to acute respiratory distress, require prompt evaluation and stabilization. Methods for management of such emergent situations will not be further discussed here.

The goals of management of AHF, as recommended by the Heart Failure Society of American, include, firstly, the improvement of symptoms of congestion, improvement of oxygenation, the optimization of volume status and minimizing side effects. The majority of patients is stable and primarily requires intravenous loop diuretic therapy for treatment of signs and symptoms of congestion.

1.3.1 Evidence and Guidelines for Management of Acute Heart Failure

Table 2 summarizes the recommendations of the Canadian Cardiovascular Society, the Heart Failure Society of America and the American Heart Association/American College of Cardiology. All three societies provide general guidelines for the care of acute heart failure. All three societies recommend adequate monitoring practices for patients receiving intravenous loop diuretics. Recommendations for monitoring patients in hospital include daily measurement of fluid balance, including fluid intake and urine output, weights taken at the same time each day, and monitoring for serum biochemistry, particularly assessment of potassium homeostasis and potential depletion, and serum creatinine as a measure of pre-renal azotemia. Vital signs are recommended to be evaluated more than once daily.
Table 2: Acute Heart Failure Management Guidelines – 2014 Summary

<table>
<thead>
<tr>
<th>Society</th>
<th>Definitions</th>
<th>Monitoring</th>
<th>Management</th>
<th>Dosage</th>
</tr>
</thead>
</table>
| Canadian Cardiovascular Society (McKelvie et al., 2013) 2013 | Acute Heart Failure - The diagnosis of AHF is based on a constellation of symptoms (e.g., orthopnea and shortness of breath on exertion) and signs (e.g., edema and respiratory crackles). Physical examination evaluates systemic perfusion and presence of congestion (cold or warm, wet or dry) | • Response to initial therapy and the need for additional therapy should be assessed less than 2 h after treatment initiation (class IIb, level C). 2006.  
• Acute renal dysfunction would generally be diagnosed when serum creatinine levels increase by more than 30% of baseline value over several days or when oliguria and rising serum creatinine are present. 2007.  
• All patients with AHF should have careful monitoring of fluid balance, including urine output, and this may require bladder catheterization (class I, level C). 2007.  
• We recommend a thorough clinical evaluation of the patient to assess their clinical hemodynamic profile (Strong Recommendation, Low-Quality Evidence). 2012.  
• We recommend that in the clinical scenario when the clinical diagnosis of AHF is of intermediate pretest probability, NP level be obtained to rule out (brain NP [BNP] 100 pg/mL; N-terminal [NT]-proBNP 300 pg/mL) or rule in (BNP 500 pg/mL; NT-proBNP 900 pg/mL if age 50-75 years, NT proBNP 1800 if age 75 years) AHF as the cause for the presenting symptoms suspicious of AHF (Strong Recommendation, Moderate-Quality Evidence). 2012.  
• Initial blood tests should include: complete blood count, creatinine, blood urea nitrogen, glucose, sodium, potassium, and troponin. 2012. | • No specific recommendations | • We recommend intravenous diuretics be given as firstline therapy for patients with congestion (Strong Recommendation, Moderate-Quality Evidence). 2012.  
• We recommend for patients requiring intravenous diuretic therapy, furosemide may be dosed intermittently (e.g., twice daily) or as a continuous infusion (Strong Recommendation, Moderate-Quality Evidence). 2012. | • In heart failure patients not responding adequately to more than 240 mg intravenous furosemide daily, treatment options include:  
– More frequent or higher doses of intravenous boluses of diuretic (class IIb, level C);  
– Combination with thiazide diuretic, eg, hydrochlorothiazide or metolazone (class IIA, level B); or  
– Continuous intravenous furosemide infusion (class IIa, level B). 2007 |
Table 2: Acute Heart Failure Management Guidelines – 2014 Summary continued

<table>
<thead>
<tr>
<th>Society</th>
<th>Definitions</th>
<th>Monitoring</th>
<th>Management</th>
<th>Dosage</th>
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<tr>
<td>American Heart Association/ American College of Cardiology (Yancy et al., 2013) 2013</td>
<td><strong>Acute Heart Failure</strong> - There is no widely accepted nomenclature for HF syndromes requiring hospitalization. Patients are described as having “acute HF,” “acute HF syndromes,” or “acute(ly) decompensated HF”; while the third has gained greatest acceptance, it too has limitations, for it does not make the important distinction between those with a de novo presentation of HF from those with worsening of previously chronic stable HF</td>
<td><em>The effect of HF treatment should be monitored with careful measurement of fluid intake and output, vital signs, body weight that is determined at the same time each day, and clinical signs and symptoms of systemic perfusion and congestion. Daily serum electrolytes, urea nitrogen, and creatinine concentrations should be measured during the use of intravenous diuretics or active titration of HF medications. (Level of Evidence: Class I, C). 2013.</em>&lt;br&gt;*<em>Performance measures based on professionally developed clinical practice guidelines should be used with the goal of improving quality of care for HF. (Level of Evidence: Class I, B). 2013.</em></td>
<td><em>Patients with HF admitted with evidence of significant fluid overload should be promptly treated with intravenous loop diuretics to reduce morbidity. (Level of Evidence: Class I, B). 2013.</em>&lt;br&gt;*<em>When diuresis is inadequate to relieve symptoms, it is reasonable to intensify the diuretic regimen using either: a. higher doses of intravenous loop diuretics (Level of Evidence: B); b. addition of a second (eg, thiazide) diuretic. (Level of Evidence: Class IIa, B). 2013.</em></td>
<td><em>If patients are already receiving loop diuretic therapy, the initial intravenous dose should equal or exceed their chronic oral daily dose and should be given as either intermittent boluses or continuous infusion. (Level of Evidence: Class I, B). 2013.</em></td>
</tr>
</tbody>
</table>
Table 2: Acute Heart Failure Management Guidelines – 2014 Summary continued

<table>
<thead>
<tr>
<th>Society</th>
<th>Definitions</th>
<th>Monitoring</th>
<th>Management</th>
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<tbody>
<tr>
<td>Heart Failure Society of America (Heart Failure Society of et al., 2010)</td>
<td>No clear definition</td>
<td></td>
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<td></td>
<td></td>
<td>Biochemistry</td>
<td>Weights</td>
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<td></td>
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<td>• When the diagnosis is uncertain, determination of plasma B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NTproBNP) concentration is recommended in patients being evaluated for dyspnea who have signs and symptoms compatible with HF. (Strength of Evidence = A). 2010.</td>
<td>• Monitoring of daily weights, intake, and output is recommended to assess clinical efficacy of diuretic therapy. (Strength of Evidence = C). 2010.</td>
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<tr>
<td></td>
<td></td>
<td>• It is recommended that serum potassium and magnesium levels be monitored at least daily and maintained in the normal range. More frequent monitoring may be necessary when diuresis is rapid. (Strength of Evidence = C). 2010.</td>
<td>• Determine after voiding in the morning</td>
</tr>
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<td></td>
<td></td>
<td>• Vital signs monitoring recommended more than daily. (Strength of Evidence = C). 2010.</td>
<td>• Account for possible increased food intake due to improved appetite</td>
</tr>
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<td></td>
<td></td>
<td>• Serum sodium monitoring recommended at least daily. (Strength of Evidence = C). 2010.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Renal function (BUN, Creatinine) monitoring recommended at least daily. (Strength of Evidence = C). 2010.</td>
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<td></td>
<td></td>
<td>• Fluid restriction (&lt;2 L/day) is recommended in patients with moderate hyponatremia (serum sodium&lt;130 mEq/L) and should be considered to assist in treatment of fluid overload. (Strength of Evidence = C). 2010.</td>
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<tr>
<td></td>
<td></td>
<td>• A low sodium diet (2 g daily) is recommended for most hospitalized patients. (Strength of Evidence = C). 2010.</td>
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1.3.2 Loop Diuretics

As indicated in Table 2 a mainstay of treatment for acute heart failure is to relieve symptoms of congestion achieved with the use of loop diuretics. During admission to hospital for acute heart failure, management of extravascular fluid volume overload is commonly achieved with intravenous (IV) loop diuretics. The Acute Decompensated HEart Failure National REgistry (ADHERE) showed that 88% of patients admitted to hospital with HF receive IV loop diuretics (W. F. Peacock et al., 2009). Although it is possible to relieve symptoms of congestion with oral loop medication, congestion requiring admission to hospital is usually treated with intravenous administration of loop diuretics. Commonly used loop diuretics are furosemide, torsemide and bumetanide, with furosemide being the most commonly used (Leto, Aspromonte, & Feola, 2014; Wargo & Banta, 2009). There is, however, limited data on the comparative efficacy of these loop diuretics in the setting of treatment of heart failure (Muller, Gamba, Jaquet, & Hess, 2003; M. D. Murray et al., 2001; Patterson, Adams, Applefeld, Corder, & Masse, 1994; Wargo & Banta, 2009).

1.3.2.1 Mechanism of Action

Intravenous loop diuretics act on the thick ascending limb of the loop of Henle, preventing sodium chloride reabsorption through the blockade of the Na-K-2Cl carrier and the inhibition of active chloride transport (Matzke & St Peter, 1990; Rose, 1991). The excretion of sodium chloride causes a decrease in the high medullary osmolality, which in turn decreases water reabsorption. Loop diuretics are capable of excreting up to 25% of filtered sodium. Additionally, increased excretion of sodium chloride causes enhanced sodium-potassium exchange in the distal part of the nephron, leading to increased potassium excretion (Matzke & St Peter, 1990).
The bioavailability of oral loop diuretics, more specifically furosemide, is extremely variable – 10 to 90% (Brater, 1998; M. D. Murray, Haag, Black, Hall, & Brater, 1997). The drug is protein bound and is delivered to the proximal tubule for its action. Fifty-percent of the drug is then excreted in the urine unchanged and the other 50% in metabolized in the kidney. One of the consequences of congestion is edema of the gastrointestinal tract, which in turn may further decrease absorption of orally administered loop diuretics, making it difficult to achieve efficacious serum concentrations of the drug (Vasko, Cartwright, Knochel, Nixon, & Brater, 1985). Intravenous administration is thus recommended due to better and more constant drug bioavailability. The intravenous dosage equivalent is half of the oral dose.

Loop diuretics have a threshold dose and a dose-responsive effect; that is to say a minimal dose is required to elicit any effect and that effect will increase with an increase in dose. Additionally, loop diuretics reach a ceiling dose, which is a dose that causes maximal fractional sodium excretion. In patients with HF, the dose-response curve is shifted downward and to the right, which signals that the maximal fractional sodium excretion to be achieved is decreased (Brater, 1994).

### 1.3.2.2 Mode of Administration in Acute Heart Failure

Intravenous furosemide can be administered as a bolus dose or as a continuous infusion, with onset of diuresis occurring after 5 minutes; peak of diuresis at 1 to 2 hours (Brater, 1998; Rose, 1991). When administered as a bolus dose, the maximum effective dose in serum is reached more quickly and therefore sodium excretion peaks at 2 hours, gradually decreasing until the next bolus dose is given (Brater, 1998). A continuous infusion of furosemide allows for a steady excretion of the drug, which thus maintains a more constant rate of sodium excretion (Wilcox et al., 1983). When this mode of administration is chosen, a bolus is usually given first.
in order to achieve a therapeutic drug concentration faster. The superiority of one mode of administration of IV furosemide over the other has long been debated (Alqahtani, Koulouridis, Susantitaphong, Dahal, & Jaber, 2014; Dormans et al., 1996; Salvador, Rey, Ramos, & Punzalan, 2005; Thomson et al., 2010) and the current best evidence comes from a recent large clinical trial as well as a meta-analysis. The DOSE (Diuretic Optimization Strategies Evaluation) trial was the first large-scale multicenter double-blinded randomized trial to determine whether an IV bolus or continuous infusion mode of administration of furosemide was better (Felker et al., 2011). A second goal of this trial was to evaluate whether a low-dose approach (equivalent to the patient’s oral dose) or a high-dose approach (2.5 times the oral dose) led to better outcomes. A total of 308 patients were enrolled in the trial and assigned to either low or high dose furosemide, and either bolus dosing or continuous infusion in a two by two factorial design. Patients were selected with the following criteria: admission to hospital with the primary diagnosis of acute heart failure (based on appropriate symptoms and physical signs), an established history of chronic heart failure, and a home dose of oral furosemide taken for at least 1 month prior to admission. Patients were excluded if they exhibited hypotension (SBP<90 mmHg), elevated serum levels of creatinine (>265 micromol/liter) or the need for vasodilators or inotropic agents. Treatment was continued for 72 hours, with the treating physician having the ability to adjust diuretic therapy at 48 hours based on clinical response, with the treatment method remaining concealed. The primary efficacy endpoint was the patients’ global assessment of symptoms and the primary safety endpoint was the change in serum creatinine at 72 hours. Secondary endpoints included patient-reported dyspnea, freedom from congestion at 72 hours, change in weight at 72 hours, net fluid loss at 72 hours, change in NT-proBNP at 72 hours, worsening or persistent HF, treatment failure, increase in creatinine >0.3mg/dL after 72 hours, and length of stay (LOS). The results of
the trial showed that there were no significant differences in either primary endpoints when comparing the mode of administration (IV bolus versus continuous infusion) or the furosemide dose (high versus low). There were also no significant differences in secondary endpoints between the two modes of administration. Additionally, a meta-analysis performed at the National Institute for Health and Clinical Excellence Guidance (NICE) in 2014 (Dworzynski et al., 2014) that included 7 randomized control trials that evaluated differences in outcomes in patients receiving IV bolus versus IV continuous infusion furosemide. No significant differences were found in outcomes, including weight loss, urine output or change in renal function and therefore the recommendation stated that either strategy can be used in the management of AHF.

Therapy with intravenous administration of furosemide continues until the patient’s acute symptoms of congestion have been stabilized or eliminated, at which point it is recommended to switch to an oral dose of furosemide in preparation of discharge from hospital. Choice of discharge dose of oral furosemide depends on the patient’s previous home oral dose as well as response to intravenous dose while in hospital. Current recommendation states that the oral dose will approximately equal to twice the IV dose administered in hospital.

1.3.3 Assessment and Monitoring of Patients Receiving Intravenous Loop Diuretics

There are several practice issues to be considered with diuretic therapy in AHF including dose of diuretic, hemodynamic changes following diuresis as well as effect of the loop diuretic on kidney function. Monitoring of the patient has the goals of assessing the efficacy of furosemide and the detection of possible adverse events associated with drug.

There are several components to the proper assessment of decongestion efficacy when using IV furosemide. It is customary for physician assessment to note clinical evidence of decongestion, such as patient symptoms, evaluation of pulmonary congestion, peripheral edema
and assessment of the jugular venous pressure. Evidence of decongestion is obtained by a few objective measurements. Weight loss is currently considered the best and most objective method of measuring and documenting diuresis (O’Brien, Menon, Stephens, Mazur, & Chung, 2012). As stated in Section 1.3.1, weight should be measured at least daily, at the same time each morning, prior to eating. Other specific recommendations for the proper measurement and record of efficacy markers are described in the current recommendations in Section 1.3.1.

Serial measurements of NT-proBNP in the setting of acute heart failure treatment can be used to monitor the effect of therapy because the half-life of NT-proBNP is relatively short. However, evidence of benefit is limited and small studies have shown conflicting results (Nohria, Mielniczuk, & Stevenson, 2005), (Bhardwaj & Januzzi, 2009). The benefit is also absent in patients with certain etiologies of heart failure that present without an elevation in NT-proBNP. These include patients with mitral stenosis and constrictive pericarditis.

Detection of potential adverse events associated with diuretic therapy includes electrolyte abnormalities, including hypokalemia and hypomagnesaemia, evidence of hypotension or acute kidney injury, and metabolic alkalosis. As a potassium-wasting drug, furosemide use can lead to hypokalemia, which if left untreated, may lead to cardiac arrhythmias. The DOSE (Diuretic Optimization Strategies Evaluation) trial had a 1% incidence of hypokalemia in each of their 4 treatment groups (discussed in Section 1.3.2.2) (Felker et al., 2011). The Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial showed a similar incidence of 3% for electrolyte disturbances; this, however, included hyperkalemia, hypokalemia, hypernatremia, hyponatremia, and hyperuricemia (Bart et al., 2012). Similarly, hypomagnesaemia can lead to potentially serious cardiac arrhythmias. When diuresis occurs rapidly and intravascular fluid is quickly removed by the kidney, the rate of interstitial fluid
moving into the intravascular space is slower and therefore can lead to symptomatic or asymptomatic hypotension. When this occurs, the rate of diuresis is slowed through the reduction of furosemide dose. Recommendation for kidney function monitoring is to measure serum creatinine, as a marker of kidney function. With ongoing diuresis, decreased perfusion of the kidney causes a decrease in the glomerular filtration rate and therefore a decrease in the filtration of creatinine. Its accumulation in the intravascular space acts as a surrogate marker of kidney function. Detection of evidence of acute kidney injury is associated with worse prognosis; however, a balance must be reached between adequately diuresing a patient with AHF as well as potential kidney injury. Metabolic alkalosis is caused as a result of a combination of factors including the activation of the renin-angiotensin system, and hypokalemia, which then leads to bicarbonate retention.

1.3.3.1 Hypokalemia

As mentioned in Section 1.3.2.1, diuresis or excessive diuresis with IV furosemide can cause an increased secretion of potassium. The extent of hypokalemia seen in patients receiving IV furosemide is dependent of the dose of the loop diuretic received; higher doses are more likely to cause hypokalemia than lower doses (Gennari, 1998). Hypokalemia is defined as serum potassium < 3.5mmol/L. Patients with heart failure have an increased risk of arrhythmias, cardiac arrest and syncope, which in turn causes them to experience more complications as a result of hypokalemia (Leier, Dei Cas, & Metra, 1994). United Kingdom Heart Failure Evaluation and Assessment of Risk Trial (UK-Heart) showed that HF patients with decreased serum potassium levels exhibited higher incidence of sudden cardiac death (J. Nolan et al., 1998). Based on these findings, the UK-Heart group recommended that all patients with chronic heart failure should receive potassium supplementation. Thus the National Council on Potassium in Clinical Practice
recommends that HF patients should receive potassium supplementation if serum potassium is below 4.0mmol/L (Cohn, Kowey, Whelton, & Prisant, 2000).
2 Protocol Development

2.1 Quality of Care for AHF: The Gap Between Guideline Recommendations and Actual Delivery of Care

As discussed in Section 1.3, several guideline documents exist informing clinicians as to appropriate care for patients with AHF. However studies have shown that adherence to recommended guidelines is not always optimal (Cabana et al., 1999). Objectives used to develop guideline recommendations for diuretic therapy center around principles of good quality of care. The Institute of Medicine (IOM) has defined quality of care as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge" (Lohr, 1990). The IOM further describes 6 principles that act as specific aims for quality care improvement. Care practices should be (1) safe, (2) effective, (3) patient-centered, (4) timely, (5) efficient and (6) equitable. In this thesis, two key principles of focus are safety, and timeliness. Safety refers to prevention of injury or adverse events to patients from the care they are receiving. Timeliness refers to reduction of potentially harmful delays and waits for both patients and care providers. Potential barriers to safety, and timeliness of diuretic management are now discussed.

2.1.1 Safety in Diuretic Management

An important implication for inclusion of monitoring practices in guideline directed care of patients treated with loop diuretics is the potential for harm with respect to electrolyte derangement, hemodynamic compromise and renal injury. Evidence from the Medicare Patient Safety Monitoring System database in the United States has shown that between 2005 and 2011 the rate of adverse events in patients admitted to hospital with AHF has significantly declined; however, mortality risk and length of stay in hospital remains significantly higher in patients
who experienced adverse events in hospital (Wang et al., 2014). The safe administration of diuretics is thus dependent on assessment of safety markers that inform the need for readjustment of therapy.

Effective diuresis occurs over days (Bart et al., 2012; Felker et al., 2011) with the potential for involving several caregivers. As such, continuity of care, or lack thereof, by physicians or by bedside caregivers may affect safety. In the Canadian academic hospital environment, the clinical teaching unit (CTU) is the predominant model of inpatient care. The clinical teaching unit consists of several physicians, including an attending staff physician, several medical residents and students. Although evidence exists to show the benefits of CTUs, several barriers to quality care of patients have also been identified in numerous studies. These include physicians of different degrees of experience (Lindenauer et al., 2007; Pattani, Wu, & Dhalla, 2014; Volpp & Grande, 2003) as well as frequent handoffs between physicians (Arora, Johnson, Lovinger, Humphrey, & Meltzer, 2005; Gandhi, 2005; Horwitz, Moin, Krumholz, Wang, & Bradley, 2008; Petersen, Brennan, O'Neil, Cook, & Lee, 1994; Philibert, 2009; Press, 2001). A handoff is defined as “the exchange between health professionals of information about a patient accompanying either a transfer of control over, or of responsibility for, the patient.” (Cohen & Hilligoss, 2010; Keyes, 2000). Proper handoffs between physicians are crucial to providing appropriate continuity of care and high quality safe patient care (Starmer et al., 2014). A systematic review focusing on physicians’ handoffs was conducted in 2009 with the goal of identifying barriers and proposed strategies (Riesenber et al., 2009). In the 46 studies that met inclusion criteria, the most common handoff barrier identified in 31% of cases was communication. Of the handoff strategies proposed in the studies included in the review, the most common strategy category was standardization (44.3%), which has shown evidence of
being beneficial to improving quality care (Burgmeier, 2002; Luther et al., 2002). The conclusion stated that inadequate physicians’ handoffs have detrimental consequences; however, high quality handoff outcome studies are needed as well as strategies for best practices (Cohen & Hilligoss, 2010). Similarly, challenges have also been identified in handovers between the nursing staff (Ebright, Urden, Patterson, & Chalko, 2004; Hays, 2003).

An additional consequence of the CTU structure that contributes to delays in communication, is the inability to identify the specific roles played by multiple physicians, including the most responsible physician (MRP). One study, performed in an academic U.S hospital, showed that a barrier rated highly by nurses was difficulty in being able to identify the MRP (O’Leary, Ritter, et al., 2010). Further significance and evidence on interprofessional communication is discussed in Section 2.1.2.

2.1.2 Timeliness of Diuretic Management

As stated in Section 2.1, timeliness of care refers to the reduction of potentially harmful delays to both patients and medical staff. This is achieved through timely reassessment of patients receiving drugs in hospital (in this case IV loop diuretics) as well as timely communication between the nursing staff and medical team on the ward. Timely communication is also commonly integrated into the concept of interprofessional collaboration (IPC); however, many variable definitions of IPC exist with limited high quality data regarding its significance (O’Leary, Thompson, et al., 2010). A Cochrane Database Review, conducted in 2009, identified 5 main elements crucial to effective IPC – “the involvement of numerous participants in care coordination, the necessity of coordination, the importance of participants having knowledge of one’s own and others’ roles, and the importance of information exchange.” (Zwarenstein, Goldman, & Reeves, 2009) This review focused on evaluation of practice-based IPC.
interventions, which were defined as “work through the incorporation of a tool or routine into practice that supports the type of interaction (e.g. communication, coordination) amongst different healthcare professionals that is thought to be necessary to improve a particular area of health care.” Results suggested that such IPC interventions improve healthcare processes and outcomes. Furthermore, multiple studies have shown that communication delays and miscommunication between the nursing and medical staff lead to errors in patient care (Baggs et al., 1999; Chassin & Becher, 2002; Leape et al., 1991; Sutcliffe, Lewton, & Rosenthal, 2004; Wilson et al., 1995). Results from the Harvard Medical Practice Study showed that, in 1133 adverse events identified in 30195 hospital patient records, inadequate reporting or communication was present as a cause in 26% of cases, inadequate follow-up of therapy in 45%, and avoidable delay in treatment in 14% of cases (Leape et al., 1991). Another study from a U.S teaching hospital, identifying medical mishaps involving medical residents, reported communication failure as a cause in 91% of instances (Sutcliffe et al., 2004).

2.2 Description of the MSH La6 Protocol and Components

2.2.1 Specific Objectives and Design of the MSH La6 Protocol

As discussed above, barriers may exist to achieving good adherence to guideline-directed practices for monitoring and drug administration, based on the structure of the medical care team and the interprofessional cooperation required. These barriers in turn may affect the safety and timeliness of intravenous diuretic therapy in hospital. The La6 Protocol was a 48-hour intervention designed to optimize the safety and timeliness of establishing effective decongestion early during admission.

To address safety particularly in a CTU setting the intervention guided appropriate patient selection. Safety was also addressed by enforcing adherence to best practices for
consistent and adequate monitoring for adverse effects of IV diuretic therapy. Safety was also addressed by directing appropriate interprofessional communication when a potentially adverse event was recorded. Literature has shown that up to 50% of drug adverse events experienced in hospital are preventable and most happen at the ordering and administering stages (Bates et al., 1995).

To address timeliness the intervention employed several strategies. Prescription of dosage and frequency of administration was evidence-based as such discouraging selection of, and persistence with, ineffective dosages. Additionally, the process of diuresis requires repeated collection and interpretation of several clinical measurement variables with a potential for delays within and between cycles of furosemide administration and reassessment. Strategies were employed to optimize interprofessional cooperation and minimize delays in reassessment and dose adjustment.

The process was entitled the Mount Sinai Hospital Lasix Protocol (MSH La6 Protocol) and consisted of 2 paper-based tools, the Physician Pre-Printed Order Set (PPOS) and the Nomogram for Stepped Diuretic Care (Nomo-SDC). The specific components of the protocol that address our objectives are now discussed.

2.2.2 Physician Pre-printed Order Set (PPOS)

The Physician Pre-Printed Order Set (PPOS) was the first component of the MSH La6 Protocol (Figure 1). The goals of the PPOS were to provide appropriate patient selection criteria, based on contemporary evidence supporting multi-dose delivery of IV furosemide and best practices for monitoring of safety and efficacy. The PPOS was completed by the treating physician. Upon completion, the treating physician delegated authority to the registered nurse to
monitor the patient and administer IV furosemide for 48 hours. The PPOS was designed with the following objectives:
**Figure 1. Physician Pre-Printed Order Set (PPOS)**

First component of the MSH La6 Protocol, completed by the treating medical team. The PPOS contains criteria for patient selection, baseline patient information, alert notifications, and furosemide dosing regimen.
i) Patient Selection

The diagnosis of acute heart failure can be challenging and inclusion criteria were organized to encourage physicians to provide clinical evidence of the appropriate diagnosis (McCullough et al., 2002). A checklist method was employed by which physicians could document appropriate patient selection. These inclusion criteria were: 1) a mandatory previous diagnosis of heart failure and home dose of oral furosemide, 2) an elevated jugular venous pressure (JVP), 3) evidence of pulmonary or peripheral edema, 4) ascites, 5) two or more kilograms of weight to lose on examination, and 6) a serum NT-pro BNP of greater than 135pmol/L. The ordering physician was advised the patients were suitable if they met the mandatory criteria as well as at least one other clinical criterion. The PPOS also specified exclusion criteria to prevent use of the protocol in patients who were not included in clinical trials of multi-dose furosemide administration. These were as follows: 1) patients with a new diagnosis of heart failure on admission and 2) those who are furosemide naïve (no home dose of oral furosemide). Caution for use was noted for those with a systolic blood pressure of less than 90 mmHg and/or with a serum creatinine greater than 260 micromol/L.

ii) Standardized Orders for Monitoring Efficacy and Detection of Drug-Related Adverse Events

Firstly, the PPOS required documentation of baseline patient information, including home dose of furosemide, weight on arrival to the ward, as well as baseline SBP, serum creatinine and serum potassium. The PPOS then provided standardized orders for daily weights, serum biochemistry, vital signs and monitoring of urine output. The PPOS also provided specific criteria that automatically suspended the process and mandated notification of the physician team for reassessment (termed ‘alert notifications’). As noted in section 2.1.1 (Safety
of Diuretic Management) the PPOS recommended specific thresholds by which the potential adverse effects of diuretic therapy could be identified. For all patients, these thresholds included a serum sodium less than 125 mmol/L and a SBP less than 90mmHg. The PPOS recommended an alert notification for serum creatinine determined based on an increase of 35% from the patient’s initial creatinine measurement. Finally, the PPOS also recommended an alert notification for serum potassium measurement above a threshold prespecified by the MD. The standardized orders for monitoring and pre-specified alert notifications were designed to identify and prevent potential adverse events associated with IV furosemide therapy.

Next, the PPOS established an efficacy target and managing strategies. Based on weight recorded on ward admission, physicians prespecified a target weight loss of at least 2kg to be achieved after 48 hours of therapy. Diet and fluid restriction orders were also enforced and gave the ordering physician a choice in a low sodium diet of less than 2 or 3 grams per day (Heart Failure Society of et al., 2010; Yancy et al., 2013) and a fluid intake of 1500 or 2000 ml per day (Yancy et al., 2013). IV doses received in the emergency department prior to admission were also recorded.

iii) Furosemide Dosing Regimen

Two principles, 1) consideration of renal function (estimated glomerular filtration rate < or > 60ml/min) and 2) administering an IV dose at least equivalent to the total daily oral loop diuretic dose, guided selection of a lower or a higher dosing schedule. For patients without renal insufficiency or a relatively small home dose of furosemide, a lower dosage regimen of 40mg IV was chosen. If renal function was impaired or the home dose of furosemide above 80mg daily, the higher dosing regimen, of 80mg IV was selected. Importantly, the DOSE trial (Felker et al., 2011) (discussed in Section 1.3.2.2) established that multiple bolus administration was as
effective as a continuous infusion with acceptable safety in the context of a randomized clinical trial. As such, 4 cycles of furosemide administration and assessment of efficacy and surveillance for adverse effect occurs within a 48-hour period. Therefore, a key design element of the Nomo-SDC was the use of twice daily bolus administration to coordinate actions of the Nomo-SDC with a standard 12-hour nursing shift.

iv) Delegation to Nursing Staff

Once the patient’s eligibility was confirmed, safety parameters set, and dosing regimen indicated, the treating physician authorized the bedside caregiver to initiate the algorithm and proceed with necessary monitoring and dose adjustments for 48 hours. Authorization to initiate the process required the signature of an ordering physician and the bedside caregiver.

2.2.3 Nomogram for Stepped Diuretic Care (Nomo-SDC)

The Nomogram for Stepped Diuretic Care (Nomo-SDC) was the second component of the MSH La6 Protocol (Figure 2). The Nomo-SDC was an algorithm tool designed for use by personnel at the point of care, which in our institution is the bedside registered nurse. The essential change in delivery of care required to initiate effective diuresis was designed to address two quality components. Firstly, timeliness of diuretic administration and monitoring (discussed in Section 2.1.2), more specifically to eliminate communication delays that occur in collating and acting upon data needed to administer IV furosemide. Secondly, prescription of standardized furosemide doses was designed to address efficiency of care and resource allocation. The tool allowed for moderate escalation of furosemide dosing based on bedside measures of efficacy and safety criteria without requiring additional orders from a physician. As such, the Nomo-SDC was conducted in its entirety by the bedside RNs, without physician consultation unless notification of the physician team was specified by the protocol. This change in practice consisted of two
parts: firstly, delegating authority to the bedside RN to order and administer the furosemide dose initially prescribed by the Nomo-SDC and secondly, delegating authority to the bedside RN to adjust the furosemide dose according to monitoring markers measured every 12 hours. The Nomo-SDC was designed with the following objectives:
Figure 2. Nomogram for Stepped Diuretic Care (Nomo-SDC)

Second component of the MSH La6 Protocol, completed by a registered nurse. Monitoring, electrolyte replacement, and furosemide prescription is detailed on the left half of the protocol. Corresponding documentation of clinical monitoring markers and drug dose administration is recorded on the right half of the protocol.
i) Selection, Timing, and Titration of Diuretic Dosing

Shifts for RNs begin at 8:00am and continue for 12 hours. Once ordered, the protocol was initiated at 8:00am (with the range of 7:00am and 10:00am) the following morning in order to facilitate nursing flow and increase efficiency of daily bloodwork and clinical reassessment, as well as adhere to current monitoring guidelines (McKelvie et al., 2013; Yancy et al., 2013) which state that weights should be recorded at the same time daily. If, however, the protocol was ordered outside of the above-mentioned time range, the medical team was responsible for any intravenous furosemide doses administered to the patient prior to the initiation of the protocol. The selection of doses was left up to the discretion of the treating physician. In such a case, the nursing staff initiated the nomogram the following morning.

Populating clinical markers of efficacy within the Nomo-SDC led to selection of the subsequent furosemide dose. Efficacy at 12 and 36 hours was defined as 800 ml of urine output over the preceding 12 hours. At the 12-hour reassessment, if this efficacy marker was achieved, the nomogram called for the dose to remain the same for the next time point (24-hour mark). If urine output was less than 800ml, the furosemide dose was increased by 40mg from the starting dose. Similarly, at 36 hours, if urine output was found to equal or be greater than 800ml, the dose of furosemide remained stable. If the urine output was below this value, the nurse was instructed by the nomogram to contact the treating physician. At 24 hours, reassessment of dosage occurred based on the patient’s weight and weight loss. Monitoring, according to the nomogram, required the patient to be weighed daily as stated in Section 2.2.3, a target weight to be achieved in 48 hours on protocol was preset by the prescribing physician. Weight loss was measured every 24 hours with a target weight loss to be achieved in 48 hours. This timeline was guided by similar
weight loss assessment in the NIH DOSE trial. In that study, weight loss was also measured every 24 hours, up to 96 hours (Felker et al., 2011). In addition, the treating physician allowed drug administration to occur for the first 48 hours before dose adjustment could occur based on clinical response. Three possible outcomes were possible at this time. If weight loss was found to be less than 1 kg over the previous 24 hours, the dose of furosemide was escalated based on the dose given at 12 hours. If weight loss was greater than 1 kg but less than the target weight preset in the PPOS, the dose of furosemide remained stable from the 12-hour mark. Lastly, if target weight was reached, the protocol was stopped and the medical team notified. Finally, reassessment at 48 hours was based on the target weight preset and dictated that if the target weight was not reached by 48 hours, the last dose of furosemide was given and the medical team notified of the protocol’s completion. If target weight was reached by this point, no furosemide was given, the protocol was deemed complete, and the medical team notified.

ii) Monitoring

Monitoring as prescribed by the Nomo-SDC was delegated to the nursing staff at each time point starting at initiation of the protocol. Serum sodium, potassium and creatinine were measured at initiation of the Nomo-SDC and every 24 hours until completion or termination of the protocol. The nursing staff completed additional measurements of potassium at 12 and 36 hours, if potassium supplementation was given at the previous assessment. Weight measurements were ordered by the Nomo-SDC to be completed at 0 hours, 24 hours and 48 hours, accompanied by the calculation of weight loss. This calculation further directed furosemide dose administration. Blood pressure was recorded every 12 hours. Similarly, urine output was recorded at every 12-hour point, and served as an efficacy marker at the 12 and 36-hour points, directing subsequent furosemide dose selection.
iii) Prevention, Detection and Treatment of Drug-Related Adverse Events

The Nomos-SDC also specified standardized biochemical monitoring and potassium replacement without requiring additional orders from a physician. If supplemental potassium was administered, serum potassium was repeated at 12 hours. A potassium replacement nomogram was embedded in the Nomos-SDC as shown in Figure 3.
Potassium protocol

- If K+ more than 4, no action
- If K+ 3.6 – 4, give potassium chloride (K-Dur) 40 mEq PO x 1 dose
- If K+ 3 – 3.5, give potassium chloride (K-Dur) 40 mEq PO q4h x 2 doses
- If K+ less than 3, contact MD stat

Figure 3. Potassium Replacement Nomogram

The Potassium Protocol is embedded within the Nomo-SDC. It contains details on appropriate potassium supplementation dosing depending on the risk of or severity of hypokalemia present.
iv) Completion of the Protocol and Transition to Usual Care

As noted, actions to populate the Nomo-SDC occurred every 12 hours up to and including 48 hours. Completing each 12-hour segment of the protocol resulted in either selection of the subsequent dose or identification of an alert notification that suspended the protocol and mandated reassessment by the MD. The medical team could choose to resume care within the Nomo-SDC or discontinue the protocol. Early completion of the protocol could also occur as prescribed by the Nomo-SDC if the therapeutic target for weight was achieved at 24 hours. Completion of the MSH La6 protocol required physician signature to acknowledge that further diuretic prescription and monitoring reverted to usual care and was at the discretion of the medical team. The practice of the RN reverted to usual bedside care and routine charting.

2.3 Issues of Local Implementation

The process change described was undertaken at a single center. The Mount Sinai Hospital is an academic health care facility in the metropolitan area of Toronto, Ontario Canada. These tools were developed during a 6-month process of review of the literature, consensus building to assess needs and objectives, protocol drafting and revision with input from a multi-disciplinary personnel including cardiology, hospital pharmacy, nursing administration and nursing education. At Mount Sinai Hospital, institution practice changes are reviewed by Clinical Practice Committee, Joint Health and Safety Committee, Risk Management, and Health Records, with final approval occurring from the Medical Advisory Committee. As an academic institution, in this experience, the PPO was populated and initiated by the physician care team that functioned as a CTU.

At Mount Sinai Hospital, bedside care of patients is delivered by registered nurses (RN).

2.4 Considerations for Education
2.4.1 PPOS as an Educational Tool

The Physician Pre-Printed Order Set was utilized as an educational tool in several ways. Firstly, populating the PPOS provided an explanation of the underlying rationale for patient selection. In addition to setting alert notification for MD reassessment, as discussed in Section 2.2.1, the ordering physician was provided with clinical scenarios (admission to the ICU, renal insufficiency, hypotension) that warrant caution. Furosemide dosing regimen selection was accompanied by guideline concerning the potential need for or lack of need for a continuous infusion of furosemide, based on up to date evidence (Felker et al., 2011). For each alert notification, guidelines for patient reassessment, documentation, and appropriate responses were provided. Lastly, the PPOS provided practice tips for using the loop diuretic protocol, which included an overview of AHF, an in-depth rationale for appropriate patient selection as well as additional information regarding the biochemical and clinical monitoring markers.

2.4.2 Educational Packages

Education of medical staff, including staff physicians, medical residents and students as well as nursing staff, about the implementation of a new quality improvement initiative has been shown to effectively improve learners’ knowledge and consequently confidence in performing a new practice (Boonyasai et al., 2007; Wong, Etchells, Kuper, Levinson, & Shojania, 2010). Prior to the implementation of the protocol education packages including oral, visual, and written materials were prepared and focused sessions were conducted with all active nursing staff on 2 hospital wards, as well as attending medical staff and residents. Education also required RNs to perform a mock run through of the nomogram, populating each step and following through to the next. Goals of education included the principles of therapy for decongestion in heart failure, use of net fluid balance and daily weights as monitoring parameters. On medical floors, weight
scales were inventoried and calibrated and procedures to ensure daily access to the same scale for all ambulatory and semi-ambulatory inpatients were consolidated. Following implementation, medical staff was educated with monthly in-service presentations, information posters and pocket cards to heighten awareness of the protocol and accessibility of the pre-printed order set. Two hospital pharmacists, thoroughly educated on the MSH La6 Protocol were also available to support medical and nursing staff. The decision to use the protocol was left at the discretion of the attending physician and clinical team. No additional clinical resources and no changes in nurse to patient ratios were engaged in this process.
3 Hypothesis and Research Aims

The purpose of this quality improvement intervention was to identify current barriers to safe and timely administration of intravenous furosemide to AHF patients and address them with the implementation of a nurse-run clinical algorithm in the first 48 hours after admission to hospital. The hypothesis stated that quality of care would improve in these patients with the use of the MSH La6 Protocol by addressing several issues. Firstly, the protocol would improve adherence to guideline-directed monitoring of AHF patients by setting prespecified, guideline recommended markers to be measured by the RN every 12 hours in order to assess safety and clinical progress of the patient. Secondly, the Nomogram for Stepped Diuretic Care would aim to improve evidence-based furosemide dose selection and administration as well as streamline interprofessional communication among medical and nursing staff.

In order to test this hypothesis, a pre and post, time series design was used to evaluate adherence to guideline-directed monitoring of AHF patients. Data was collected for 32 months prior to the implementation of the protocol and for 8 months after. Opportunity-based scores, all-or-none scores (defect-free scores), and Shewhart control charts were used for specific measurements. Safety of the protocol was measured through adherence to specific algorithm steps using the above-mentioned scores, as well as incidence of adverse events, which included hypokalemia and acute kidney injury. Incidence of adverse clinical events was also recorded, including death or transfers to an acute care setting, and protocol suspension. Furosemide prescription was measured by recording IV furosemide doses given in the first 24 hours of hospital admission, second 24 hours and total over 48 hours. Details of evaluation are discussed in Section 4.
4 Methods of Evaluation

4.1 Overview of Quality Improvement Assessment

Quality improvement in health care is based on the principle that there is an opportunity for improvement in every process that occurs in medical practice (Berwick, 1998). In Evaluating the Quality of Medical Care, Donabedian suggested the quality of health care could be measured by assessing its structure, processes and outcomes (Donabedian, 2005). Several strategies of quality improvement exist, and include intervention at the level of the provider and at the level of the patient. Quality improvement strategies include, but are not limited to, facilitated relay of clinical data to providers, provider education, and organizational change (Shojania, McDonald, Wachter, & Owens, 2004). The protocol evaluated in this project encompassed an organizational change that altered the relationship between multidisciplinary providers (the bedside RN and the ordering physician) and included several interventions for the providers. The process drove utilization of best practice, and strategies utilized include uptake of an algorithmic tool for decision support, provider education, and mandated population of quality indicators. Two dimensions of quality were assessed in this project are safety, defined as patient care that is free of potential adverse events, and timeliness, defined as patient care that is free of delays and waits (Lohr, 1990) (further discussed in Section 2.1). The evaluation of this intervention fits into a model of a feasibility study (Bowen et al., 2009). Studying the feasibility of a new evidence-based intervention answers questions about its possible efficacy, effectiveness, and future directions. In the case of the MSH La6 protocol, the feasibility evaluation performed addressed three of eight possible areas of feasibility focus, and included implementation, integration and limited-efficacy testing. The methodology for process measurement and outcome assessment are presented in this chapter. Specific results for the evaluation are presented in Chapters 5 and 6.
4.2 Process Measurement

Process measurement in a quality improvement project is crucial to understanding the effects of that project on the system where it is implemented. Process measurement consists of understanding the process and outcomes of a starting system, the implementation of the initiative, and the monitoring of changes made through the implementation of the initiative ("Measurement for Quality Improvement," 2013). Proper measurement of a process is vital to its success.

4.2.1 Measuring Adherence to a Process

Evaluation of a change to the provision of health care requires assessment of feasibility in order to understand if the intervention is being implemented as intended. To implement the Nomo-SDC appropriately, several actions by more than one caregiver over a specified duration within the algorithmic tool had to be performed correctly. Safety of the process was also predicated on timely and appropriate population of the Nomo-SDC. Therefore, methodology to measure the adherence was selected. Adherence to any process can be evaluated using objective measures of performance in providing quality care. A composite performance measure is defined as a value encompassing multiple indicators of provider or healthcare performance required in a process (Peterson et al., 2010). A composite value summarizes and allows for evaluation of a complex process, in this case adherence to a multi-step, longitudinal clinical algorithm.

Evaluation of the MSH La6 Protocol included the opportunity-based composite score and the all-or-none composite score.

4.2.2 Opportunity-based scoring

Opportunity-based scoring within a process is defined as the proportion of completed individual process measures that are mandated. The score is calculated by dividing the number of
times a process measure was completed (or given) over the number of times a process measure was prescribed or mandated (Peterson et al., 2010). The advantage of an opportunity score is the proportional weight of each individual measure based on the number of times it is prescribed. However, this can potentially lead to a disadvantage if the most common individual process measures are not the most important but greatly influence the composite score with a higher weight proportion.

4.2.3 All-or-none Scoring/Defect-Free Scoring

All-or-none scoring (also known as defect-free scoring) is defined as the proportion of patients that receive all process measures for which they are eligible (Peterson et al., 2010). This type of score is also defined as proportion of patients that receive perfect care and therefore measures performance on a patient level. The advantage of a defect-free score is the inherent emphasis on excellent care (T. Nolan & Berwick, 2006). The disadvantage is that this score could potentially simplify a complex process and omit important achievements within it.

4.2.4 Shewhart Control Charts

Shewhart control charts, also known as statistical process control charts, are a type of an analytical tool used to detect variation in a process. They were originally developed by Walter Shewhart to measure performance in the manufacturing industry (Shewhart, 1931). Two types of variation are detected using a control chart: common cause variation and special cause variation (Mohammed, Cheng, Rouse, & Marshall, 2001). Common cause variation is intrinsic to any process and points to the process being in statistical stability. Special cause of variation is found because of an extrinsic factor acting on the process and changing it. Shewhart control charts are plotted with time on the x-axis, and the measurement in question on the y-axis (Benneyan, Lloyd, & Plsek, 2003; Mohammed, Worthington, & Woodall, 2008). Three additional lines are
also present. The central line indicates the mean of the data and 2 additional lines demonstrate the upper and lower control limits, usually placed 3 standard deviations (SDs) away from the mean. If all data points are confined within the control limits, the process is considered to be stable, displaying common stable variation. If a data point or multiple data points fall outside of the control limits, Shewhart rules are used to look for special causes of variation. Eight consecutive data points showing evidence of unstable variation represent a sustained change in the process and a new mean central line is calculated for the process.

Until the late 1980s control charts were used for primarily monitoring quality in industrial sectors. At that time, however, interest gained in the healthcare sector and Shewhart control charts increased in utilization. Although potential benefits in using control charts in evaluation of processes were demonstrated (Glasziou, Irwig, & Mant, 2005), gathered interest was moderate and mostly applied in monitoring hospital performance and public health observation (Benneyan, 1998; Mohammed et al., 2001; Morton et al., 2001). In 2007, 2 systematic reviews were conducted by groups in England (Tennant, Mohammed, Coleman, & Martin, 2007) and Sweden (Thor et al., 2007) to evaluate the use of control charts in monitoring clinical variables in patients, with results highlighting that control charts were found to be simple and effective with good sensitivity and specificity characteristics (Tennant et al., 2007). The conclusion stated that this form of evaluation was promising but largely underutilized.

To evaluate the impact of the MSH La6 Protocol, Shewhart control charts were used to determine whether process measures of heart failure care changed over time during the 32 months pre-implementation of protocol and for 8 months after.

4.3 Selection of Endpoints for Process Measurement

4.3.1 Selection of Safety Endpoints
Safety of the MSH La6 Protocol was evaluated in several ways. The concept of safety within such practice change encompassed several components, including adherence to monitoring actions prescribed by the Nomo-SDC (further discussed in Sections 2.2.1 and 2.2.2), and potential clinical adverse events. These components are described in greater detail below.

i) Adherence to Monitoring Actions

As noted in 3.2.1, safety of the process was predicated on adherence to the actions for patient monitoring prescribed by the Nomo SDC, throughout the duration of treatment on the MSH La6 Protocol. The Nomo-SDC monitoring actions were ideal for consideration as opportunities for care and therefore an opportunity-based score was calculated for 1. Daily weight measurement, 2. Total daily urine output, 3. Blood pressure, 4. Daily measurement of serum sodium, 5. Daily measurement of serum potassium, and 6. Daily measurement of serum creatinine. A composite opportunity-based score that combined all of the above individual measures was also calculated. A composite opportunity-based score was also calculated per patient, where up to 23 monitoring care processes were included to derive a monitoring completion score for each patient. Each patient had a different number of total monitoring care processes deemed eligible because the duration of the protocol varied based on each individual case. The maximum number of 23 monitoring care processes was calculated if the patient was placed on protocol for a full 48 hours. Patient level care was considered by deriving an all-or-none score (or a “defect-free score”), defined as the proportion of patients receiving all of the pre-specified care processes for which they are eligible (Peterson et al., 2010). Thus, this score reflected the proportion of patients receiving ‘perfect’ care. Adherence measured in this manner was performed in a sample of patients treated with the La6 Protocol and presented in chapter 4.
The actions prescribed in the Nomo SDC simply describe an optimal standard of care, as described in Section 1.3.1, that also applies to any patient admitted for acute heart failure receiving intravenous diuretic therapy for relief of congestion. Therefore, similar metrics to evaluate processes of care were applicable to patients receiving usual care, either prior to implementation of the La6 Protocol or for whom the protocol was not employed. Adherence to daily monitoring of patients receiving IV loop diuretics as currently recommended by major cardiovascular societies was evaluated. Monitoring measures comprising the composite score included daily serum potassium, daily serum creatinine and daily ward weight. Compliance to these measures was determined using two methodologies, opportunity-based scoring (discussed in Section 4.2.2) and all-or-none scoring (discussed in Section 4.2.3). The composite opportunity-based score was calculated as the total number of monitoring measures completed divided by the total number of actions required (3 daily measurements; baseline, 24 and 48 hours).

Additionally, the proportion of patients with a minimum of 2 ward weight measurements in the first 48-hour was calculated as a minimum pre-requisite measure that demonstrated diuretic progress was being monitored. All process measures were also expressed as group means calculated each consecutive month throughout the pre- and post- implementation time periods. By evaluating these opportunities for care in a similar manner, an evaluation of overall variation in care was possible using Shewhart control charts. These results are presented in Chapter 5.

**ii) Definition of potential adverse events: potassium homeostasis**

The significance of potassium homeostasis and the consequences of its disruption were discussed in Section 1.3.3. Thus, abnormalities of serum biochemistry were examined over the 0-
24h and 24-48h interval of the protocol. Hypokalemia was considered an adverse effect of diuretic therapy and was classified as: severe hypokalemia (serum K$^+ < 3.0$ mmol/L, considered a serious adverse event), hypokalemia (serum K$^+ \geq 3.0$ and <3.5 mmol/L), and a risk of hypokalemia (serum K$^+ \geq 3.5$ and <4.0 mmol/L). Since potassium replacement was included in the Nomo-SDC, hyperkalemia (serum K$^+ > 5.0$ mmol/L) was also considered a serious adverse event.

**iii) Definition of potential adverse events: renal function**

A rise in serum creatinine >50% above baseline at anytime was considered a serious adverse event, based on the RIFLE criteria for acute kidney injury (AKI). The RIFLE Criteria (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) is a classification system developed in 2004 that stratifies the severity of acute kidney injury based on the increase of serum creatinine, or decrease of estimated glomerular filtration rate (eGFR), or decrease of urine output (Bellomo et al., 2004). The severity of AKI is graded based on the following rules:

- **Risk** – 50% increase in the serum creatinine, or a decrease in GFR by 25 percent, or urine output <0.5 mL/kg per hour for six hours.
- **Injury** – 100% increase in the serum creatinine, or a decrease in GFR by 50 percent, or urine output <0.5 mL/kg per hour for 12 hours.
- **Failure** – 300% increase in the serum creatinine, or a decrease in GFR by 75 percent, or urine output of <0.3 mL/kg per hour for 24 hours, or anuria for 12 hours.
- **Loss** – Loss of kidney function for more than 4 weeks.
- **ESRD (End-Stage Renal Disease)** – Loss of kidney function for more than 3 months.

For evaluation of protocol safety, presence of AKI was assessed through change in serum creatinine in the RIFLE criteria.
iv) Adverse Clinical Events

Identification and prevention of adverse events are particularly important due to the above-discussed issues of safety and timeliness of therapy but also due to the high mortality risk of AHF. Canada’s in-hospital mortality rate was found to be 9.5 deaths per 100 patients in their index hospitalization in the late 1990s (Lee et al., 2004). In Ontario, that rate was 9.2. The age- and sex-adjusted in-hospital mortality rate significantly increased for patients over 75 years of age.

In evaluating the MSH La6 Protocol, several adverse clinical events were considered critical and were recorded. Deaths or transfers to a higher acuity setting during use of the protocol were recorded. Events in which the protocol was suspended unexpectedly or by an alert notification were recorded. The alert notifications included a rise in serum potassium >5.0mmol/L, serum sodium <125mmol/L, systolic BP <90mmHg, and a rise in serum creatinine of at least 30% above baseline.

4.3.2 Selection of Endpoints for Outcome Measurements

i) Furosemide Administration

The organizational change mandated by treatment in the La6 Protocol was to improve timeliness of furosemide administration and the appropriate patient assessment required. Therefore, amounts of furosemide administered to patients treated within the Lasix protocol were assessed by evaluating adherence to protocol furosemide prescription. Adherence to the Nomo-SDC-prescribed administration of furosemide was expressed as the ratio of the dose administered compared to the planned dose ordered by correct interpretation of the Nomo-SDC. Opportunity-based scoring was calculated for each patient based on up to 6 opportunities the bedside RN had to administer furosemide over the duration of the protocol. From initiation of the protocol, six
opportunities for furosemide administration included 0 hours, 6 hours, 12 hours, 24 hours, 36 hours and 48 hours on protocol. The opportunity-based score was reported for the entire cohort. An all-or-none score, based on patients receiving every pre-specified furosemide dose in the correct amount was also calculated.

To assess impact of the La6 Protocol on furosemide administration, total furosemide doses given were recorded in the 0-24 hour block, 24-48 hour block and 0-48 hours in the pre- and post-implementation cohorts. The proportion of patients who had an increase in furosemide dose in the second 24-hour block was determined.

ii) Potassium Administration

Adherence to potassium replacement was examined in a similar fashion to adherence to furosemide administration. Replacement for hypokalemia or risk of hypokalemia, was calculated as an opportunity-based score for any supplementation administered for serum potassium <4.0mmol/L. An all-or-none score was calculated based on the correct dosage given for the appropriate pre-specified threshold of serum potassium at the correct time.

4.4 Study Design

4.4.1 Pre and Post Design

The pre-implementation cohort was retrospective and collected from the EPR system at Mount Sinai Hospital. This cohort represented the standard routine practice at the institution provided to AHF patients. Patients admitted to hospital with the primary diagnosis of AHF were identified, to be compared to the post-implementation group after the rollout of the protocol. The key advantage of this cohort was that patients in this group were not affected or biased with the use of the protocol. This group represented the real world approach to the treatment of AHF at a tertiary academic institution.
The implementation of the protocol and its evaluation was performed as an observational, prospective cohort study. The post-implementation group was thus collected prospectively and similarly, included all patients admitted to MSH with the primary diagnosis of AHF. The use of the protocol was left at the discretion of the treating physician. Although the La6 Protocol has specific and evidence-based inclusion and exclusion criteria, it was recognized that the treating physician, examining the patient on admission, was best quipped to make the proper clinical judgment about eligibility of the protocol in each specific case. This provided the advantage of evaluating the impact of the protocol in a real-world setting and test true uptake and effect.

Although formal scientific experiment designs, such as randomized control trials (RCTs), are highly valuable in testing important hypotheses and do so with as little bias as possible, a set of specific challenges come with testing the impact of a process change (Berwick, 1998). Process related interventions are specifically complex and impart their influence in a specific setting and on an entire process. By definition, a formal study design such as an RCT is meant to disperse the majority of the ‘noise’ of a real world system, in order to allow the independent variable of interest to produce a signal. This, however, comes to a disadvantage when variation in an entire system (or process) is to be tested.

4.4.2 Patient populations

The pre-implementation cohort was assembled using the EPR system to retrospectively identify all patients admitted with a primary diagnosis of AHF over a 32-month period prior to the implementation of the MSH La6 Protocol between March 3rd, 2010 and October 24th, 2012. Inclusion criteria was composed of 1) patients admitted to MSH with a primary diagnosis of AHF who had received at least one dose of bolus intravenous (IV) furosemide within 24 hours of admission. Patients who received a continuous infusion of furosemide within the first 48 hours of


admission to hospital and/or those who did not received at least one dose of bolus IV furosemide within 24 hours of admission were excluded. The post-implementation cohort was collected prospectively and consisted of all consecutive patients admitted to MSH with the primary diagnosis of AHF over 8 months between July 1st, 2013 and February 27th, 2014. The same inclusion and exclusion criteria for the pre-implementation were used to select the post-implementation cohort and therefore included patients who were treated using the protocol, and patients who received routine care.

The entire population from both the pre- and post-implementation cohorts was also evaluated as eligible or ineligible for treatment by the MSH La6 protocol, based on the inclusion and exclusion criteria specified in the PPOS, regardless of whether patients were treated using the protocol or not. Finally, the implementation cohort consisted of consecutive patients treated using the La6 Protocol between December 15th, 2012 and June 30th, 2013.

4.4.3 Data collection

In the post implementation cohort, charts of all patients admitted with a primary diagnosis of AHF were prospectively reviewed daily, regardless of La6 Protocol use. Patient data was collected from multiple sources over the first 48 hours after admission to hospital. For those patients placed on the La6 Protocol, the PPOS and the Nomo-SDC were also collected for analysis. Information on patient’s presentation to hospital was collected from physician and nursing notes in the emergency department (ED). This data was comprised of date and time of presentation and admission to hospital, patient’s vital signs including blood pressure, heart rate, respiratory rate and oxygen saturation level, weight measurement, intravenous furosemide dose and time of administration and total ED urine output and time of measurement. Bloodwork done in the ED was collected from the patient’s electronic patient record (EPR) and the following
markers recorded – hemoglobin, hematocrit, white cell count, platelets, sodium, potassium, urea, creatinine, estimated glomerular filtration rate (eGFR), bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, international normalized ratio (INR), serum B-type natriuretic peptide (BNP), and troponin. Data on the patient’s medical and social history was collected from a consultation note written by a physician in the ED. Recorded history included date and time of consultation, a previous recorded history of chronic heart failure and date of diagnosis (if available), admission to hospital with the primary diagnosis of AHF in the previous year, history of percutaneous coronary intervention (PCI), myocardial infarction (MI), aortocoronary bypass (ACB), pacemaker or defibrillator, diabetes, hypertension, or smoking. Clinical signs and symptoms of the patient’s presentation to the hospital were recorded and included symptoms of fatigue, dyspnea, orthopnea, and paroxysmal nocturnal dyspnea (PND) as well as clinical signs of peripheral edema, and a jugular venous pressure (JVP) measurement. Patient’s list of home medications and dosage that were recorded included a loop diuretic, thiazide diuretic, spironolactone or eplerenone, angiotensin converting enzyme (ACE) inhibitor, angiotensin II receptor antagonist, β-adrenergic receptor antagonist, digoxin, calcium channel blocker, anti-arrhythmic medication, anti-platelet medication, anti-coagulation medication, vasodilator medication, or lipid medication. This data was collected from the physician consultation note in the ED and confirmed through a hospital pharmacist note in EPR. Following admission to the cardiology or medicine ward, clinical patient data was collected for 48 hours. In each 24-hour time block data was collected from EPR on several clinical markers as well as furosemide and potassium administration. Intravenous furosemide and potassium replacement data included every ordered dose, administered dose and time of every administration. Clinical markers recorded consisted of serum sodium, potassium
and creatinine, total urine output in 24 hours, and every weight measurement recorded. Additionally, final weight measurement prior to discharge (defined as discharge weight) and length of stay were recorded for every patient.

Data collection of patients placed on protocol began from the first use of the La6 protocol during the implementation period on December 15\(^{th}\), 2012. Following completion of the implementation period on June 30\(^{th}\), 2013, during which data was collected only on patients treated using the protocol, data collection began on all patients admitted to Mount Sinai Hospital with the primary diagnosis of AHF. Data collection was completed on February 28\(^{th}\), 2014. Subsequently, patients were grouped as eligible or ineligible based on inclusion and exclusion criteria defined in the PPOS. Permission to perform prospective data collection was approved by the Mount Sinai Hospital Research Ethics Board.

Data collected for both cohorts consisted of patient demographics, home medications, serum potassium and creatinine, weight measurements, and total furosemide and potassium doses received in the first 48 hours of admission to hospital. Home medications recorded included loop diuretic, thiazide diuretic, spironolactone or eplerenone, angiotensin converting enzyme (ACE) inhibitor, angiotensin II receptor antagonist, \(\beta\)-adrenergic receptor antagonist, digoxin, or calcium channel blocker. All weight measurements taken in the first 48 hours of admission to hospital were recorded.
Table 3. Sample Data Collection Form

**DATA COLLECTION SHEET**
for PATIENTS ENROLLED IN THE PROTOCOL

**DEMOGRAPHICS**
(FACESHEET)

| Patient Identifier: ____________________ | Date of Admission (yy/mm/dd):__/__/__ |
| Age: _____ | Time of Admission (hh:mm): ___:___ |
| Sex: ☐ M ☐ F | Date of Discharge (yy/mm/dd):__/__/__ |
| Primary diagnosis: ________________ | Time of Discharge (hh:mm): ___:___ |

Ward: ______
Service Admitted: medicine | cardiology

**EMERGENCY ROOM ASSESSMENT**
(ER SHEET REVIEW)

(If patient not admitted through ER, go to consultation.)

| Presenting complaint: ________________ | Date of Registration (yy/mm/dd):__/__/__ |
| ___:___ | Triage Time (hh:mm): ___:___ |
| Weighed: ☐ Y ☐ N | Time of Registration (hh:mm): ___:___ |
| ___ kg | Time Seen (hh:mm): ___:___ |
| Heart rate: ☐ Y ☐ N | SYS/DIA: ___/___ |
| ___ bpm | Dosage: _____ mg |
| Respiration rate: ☐ Y ☐ N | Time of administration (hh:mm): ___:___ |
| ___ bpm | Volume: _____ mL |
| O₂ saturation: ☐ Y ☐ N | Time of measurement (hh:mm): ___:___ |
| ___% | __________________ |
Date of Collection (yy/mm/dd): ___/___/___

Time of Collection (hh:mm): ____:_ __

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<tr>
<td>Hematocrit (Ht)</td>
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<tr>
<td>White Cell Count</td>
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<tr>
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<tr>
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<tr>
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</tr>
<tr>
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<tr>
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<td></td>
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<tr>
<td>Albumin</td>
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</tr>
<tr>
<td>INR</td>
<td></td>
</tr>
<tr>
<td>BNP</td>
<td></td>
</tr>
<tr>
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CONSULTATION WITH FIRST MED/CARD CONTACT
(PINK CONSULT SHEET OR 1ST DOCUMENTED NOTE)

Date of Consult (yy/mm/dd): ___/___/___

Time of Consult (hh:mm): ____:_ __

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<tr>
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<td>(REFER TO PREVIOUS REPORT)</td>
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<tr>
<td>Previous ACB:</td>
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<tr>
<td>Pacemaker/Defibrillator:</td>
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</tr>
<tr>
<td>Diabetes</td>
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<tr>
<td>Medication Type</td>
<td>Medication</td>
<td>Daily Dose</td>
<td>Change in Diuretic Dose within Past 1 Month</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------</td>
<td>------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Diuretic use</td>
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<td>Loop Diuretic</td>
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<td>Ca²⁺ Channel blockers</td>
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<td>Other Vasodilators</td>
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<tr>
<td>Lipid Medication</td>
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</tbody>
</table>

**CURRENT MEDICATIONS**
WARD ADMISSION
(POWERCHART REVIEW OF 24 HOURS)

(CHECK MAR SUMMARY)

0 HOURS
Date of Admission (yy/mm/dd): ___/___/___
Time of Admission (hh:mm): __:__

Lasix Ordered

☐ Y ☐ N Dose: ____ Time: ____

Lasix Given

1st: ☐ Y ☐ N Dose: ____ Time: ____
2nd: ☐ Y ☐ N Dose: ____ Time: ____
3rd: ☐ Y ☐ N Dose: ____ Time: ____

K+ replacement

1st: ☐ Y ☐ N Dose: ____ Time: ____
2nd: ☐ Y ☐ N Dose: ____ Time: ____

Review Labs

Na+ ☐ Y ☐ N ____ mmol/L Time: ____
K+ ☐ Y ☐ N ____ mmol/L Time: ____
SCr ☐ Y ☐ N ____ μmol/L Time: ____

Urine output
(CHECK CLINICAL DOCUMENTATION)

☐ Y ☐ N ____ mL Time: ____

Weight
(ALL WEIGHTS WITHIN 24 HOURS)

☐ Y ☐ N ____ kg Time: ____
Lasix Ordered

☐ Y ☐ N  
Dose: ___  Time: ___

Lasix Given

1st:  ☐ Y ☐ N  
Dose: ___  Time: ___

2nd:  ☐ Y ☐ N  
Dose: ___  Time: ___

3rd:  ☐ Y ☐ N  
Dose: ___  Time: ___

K+ replacement

1st:  ☐ Y ☐ N  
Dose: ___  Time: ___

2nd:  ☐ Y ☐ N  
Dose: ___  Time: ___

Review Labs

Na+  ☐ Y ☐ N  ____ mmol/L  Time: ___
K+  ☐ Y ☐ N  ____ mmol/L  Time: ___
SCr  ☐ Y ☐ N  ____ µmol/L  Time: ___

Urine output

(CHECK CLINICAL DOCUMENTATION)

☐ Y ☐ N  ____ mL  Time: ___

Weight

(ALL WEIGHTS WITHIN 24 HOURS)

☐ Y ☐ N  ____ kg  Time: ___

Discharge Weight

(LAST WEIGHT ON THE WARD)

____ kg  Time + Date: ______________________
WHY PATIENT WAS NOT ENROLLED IN PROTOCOL

INCLUSION CRITERIA

- Dyspnea
- Edema
- Increased BNP (>100)
- Elevated JVP (>4cm)

EXCLUSION CRITERIA

- New diagnosis of HF
- Loop diuretic naïve
- SBP < 90 mmHg
- SCr > 260 mmol/L
- No inclusion criteria
- Treated with PO Lasix on ward

CONCLUSION

- Protocol Eligible (1 or more inclusions and no exclusions)
- Protocol Ineligible (1 or more exclusions regardless of any inclusions)
5 Improving Efficiency of Diuretic Care for Patients Hospitalized with Decompensated Heart Failure Using a Nurse Implemented Strategy: MSH La6 Protocol

5.1 Introduction

Hospitals are faced with the challenge of treating acutely decompensated heart failure (ADHF), attempting to minimize costs and length of stay while at the same time improving quality of care (Yeung et al., 2012). Processes of care should be rational and evidence based. Intravenous (IV) loop diuretic therapy remains the cornerstone of inpatient heart failure (HF) (W. F. Peacock et al., 2009) care requiring appropriate dose selection then evaluation of efficacy and adverse events in a cycle of actions that recurs throughout admission. The tasks of prescription and drug administration are commonly divided between the ordering physician team and registered nurses and carried over frequent transfer of care responsibility between both nurses and clinicians with variable levels of training (Devlin, Kozij, Kiss, Richardson, & Wong, 2014). Variation in dosing and delays in communication between caregivers may impair the efficiency of achieving diuresis.

At our institution, a practice change to optimize the efficiency of loop diuretic administration was developed and tested. The MSH La6 Protocol is a 48-hour intervention implemented early during admission with the intent of achieving high quality and efficiency of care. The objective was not to test the well-understood efficacy of loop diuretic therapy; rather to implement a process to achieve diuresis while eliminating communication delays that occur between clinical personnel. Additional objectives included standardization of furosemide
prescription and best practices for monitoring efficacy and adverse effects. The current study presents the development, initial adherence and safety of the MSH La6 Protocol.
5.2 Methods

The MSH La6 Protocol consists of 2 paper-based tools: I. Physician Pre-Printed Order Set (PPOS), and II. Nomogram for Stepped Diuretic Care (Nomo-SDC), which allows autonomous action to deliver and adjust diuretics by a bedside caregiver without delays for physician approval.

5.2.1 The Physician Pre-Printed Order Set (PPOS)

The PPOS (Figure 1) consolidated the tasks of the ordering physician, fulfilling the following objectives:

i) Patient Selection

The target population for this intervention was loop diuretic-experienced patients with a previous history of HF, for whom the primary treatment objective was relief of systemic and pulmonary venous congestion. The recommended goal of therapy was a target weight loss of $\geq 2$ kg over 48 hours. Inclusion and exclusion criteria were verified by the medical team using a checklist.

ii) Standardized Orders for Monitoring Efficacy and Safety of Therapy

The PPOS standardized orders for clinical and biochemical monitoring and importantly prespecified criteria by which scheduled diuretic therapy could proceed without physician consultation. The PPOS also specified ‘alert notifications’ for potentially dangerous situations that automatically suspended the process and mandated reassessment by the medical team. For each alert notification, guidelines for patient reassessment and documentation were provided.

5.2.2 The Nomogram for Stepped Diuretic Care (Nomo-SDC)

The Nomo-SDC (Figure 2) was an algorithm tool that allowed delivery and escalation of IV furosemide dosing based on bedside measures of efficacy and safety without physician
consultation unless notification of the physician team was specified by the protocol. In our institution, the bedside registered nurse directed the Nomo-SDC. After training, no additional clinical resources and no changes in nurse-to-patient ratios were required. The following considerations further informed the Nomo-SDC design:

i) **Timing, and Titration of Furosemide Dosing**

Recent evidence informed our approach to the safe and effective IV loop diuretic administration particularly for HF patients already established on oral loop diuretic therapy (Bart et al., 2012; Felker et al., 2011). Furosemide prescription also complied with current guidelines for the treatment of acute heart failure in hospital (McKelvie et al., 2013; Yancy et al., 2013).

Two principles, 1) consideration of renal function (estimated glomerular filtration rate < or > 60ml/min) and 2) administering an IV dose at least equivalent to the total daily oral loop diuretic dose, guided selection of a lower or a higher dosing schedule. Importantly, the NIH DOSE trial established that multiple bolus administration was as effective as a continuous infusion (Felker et al., 2011). Therefore, a key design element of the Nomo-SDC was the use of twice daily bolus administration to coordinate actions of the Nomo-SDC with a standard 12-hour nursing shift. Identifying clinical markers of efficacy within the Nomo-SDC led to selection of the subsequent furosemide dose. If urine output was < 800ml/12 hours, or weight loss was < 1kg/24 hours, an escalation of the IV furosemide dose was triggered, with subsequent reassessment occurring every 12 hours. If efficacy targets were not met by 36 hours, the Nomo-SDC compelled notification of the medical team for reassessment.

ii) **Monitoring and Replacement of Electrolytes**

Actions for monitoring electrolytes and renal function were also aligned with standard 12-hour nursing shifts. A nomogram for potassium monitoring and replacement without
physician consultation was embedded in the Nomo-SDC (Figure 2). Potassium replacement at adjusted doses was indicated for serum $K^+ < 4.0$mmol/L.

**iii) Completion or Early Termination of the Protocol**

Completing each 12-hour segment of the protocol resulted in either selection of the subsequent dose, identification of an alert notification for suspension, or therapeutic target weight loss achievement. After 48 hours, further diuretic therapy reverted to usual care and communication between the medical team and RN.

**5.2.3. Evaluation of Patient Population, Feasibility and Safety**

The decision to use the protocol was left at the discretion of the attending physician. Charts of all patients admitted with a primary diagnosis of AHF were prospectively reviewed daily, regardless of La6 Protocol use. Patients were grouped as eligible or ineligible based on inclusion and exclusion criteria defined in the PPOS. The electronic patient records were reviewed to extract presenting history, demographics, past medical and medication history including admissions for AHF, serum biochemistry and IV loop diuretic administration. Length of stay in hospital was recorded. Permission to perform prospective data collection was approved by the Mount Sinai Hospital Research Ethics Board.

The primary feasibility endpoint was the proportion of patients initiated on the La6 Protocol who then completed the entire 48 hours or reached target weight loss early while on protocol.

Safety was examined in multiple ways. Deaths or transfers to a higher acuity setting during use of the protocol were recorded. Events in which the protocol was suspended unexpectedly or by an alert notification were recorded. The alert notifications included a rise in serum potassium $> 5.0$mmol/L, serum sodium $< 125$mmol/L, systolic BP $< 90$mmHg, and a rise in
serum creatinine of at least 30% above baseline. Abnormalities of serum biochemistry were examined over the 0-24h and 24-48h interval of the protocol. Hypokalemia was considered an adverse effect of diuretic therapy and was classified as: severe hypokalemia (serum K+ <3.0mmol/L, considered a serious adverse event), hypokalemia (serum K+ ≥3.0 and <3.5mmol/L), and at risk of hypokalemia (serum K+ ≥3.5 and <4.0mmol/L)(Gennari, 1998). Since potassium replacement was included in the Nomo-SDC, hyperkalemia (serum K+ >5.0 mmol/L) was also considered a serious adverse event. A rise in serum creatinine >50% above baseline at anytime was considered a serious adverse event, based on the RIFLE criteria(Bellomo et al., 2004; Zhang et al., 2015) for acute kidney injury (AKI).

### 5.2.4 Evaluation of Protocol Adherence

The protocol was considered initiated if the PPOS was completed and at least one dose of furosemide was administered. We evaluated specific Nomo-SDC monitoring actions as opportunities for care and calculated an opportunity-based score for patient weights, urine output, blood pressure, serum electrolyte and creatinine measurements. The score was calculated as the total number of actions completed divided by the total number of actions required by the Nomo-SDC. A composite opportunity-based score of these performance measures was also calculated. A composite opportunity-based score was also calculated per patient, where up to 23 monitoring care processes were included to derive a monitoring completion score for each patient. Patient level care was considered by deriving an all-or-none score (or a “defect-free score”), defined as the proportion of patients receiving all of the pre-specified care processes for which they are eligible (Peterson et al., 2010). Thus, this score reflected the proportion of patients receiving ‘perfect’ care.
Adherence to the Nomo-SDC-prescribed administration of furosemide was expressed as the ratio of the actual dose administered compared to the planned dose dictated by correct interpretation of the Nomo-SDC. Opportunity-based scoring was calculated for each patient based on up to 6 opportunities the bedside RN had to administer furosemide over the duration of the protocol, and reported for the entire cohort. An all-or-none score, based on patients receiving every pre-specified furosemide dose in the correct amount was also calculated.

Adherence to Nomo-SDC prescribed potassium replacement was examined for hypokalemia or risk of hypokalemia, calculated as an opportunity-based score for any supplementation administered for serum potassium <4.0mmol/L. An all-or-none score was calculated based on the correct dosage given for the appropriate pre-specified threshold of serum potassium at the correct time.

5.2.5 Evaluation of Early Effectiveness

Effectiveness of diuresis was evaluated as weight loss per 24 hours on protocol. Total weight loss during admission was also recorded.

5.2.6 Statistical Analysis

Data is presented as mean ± standard deviation or median and interquartile range, as appropriate. Dose prescription, administration, and measures of adherence were compared between the 0-24 hour block and 24-48 hour block using unpaired t-tests or chi squared analysis for continuous and categorical variables, respectively. Percent changes in serum creatinine from the baseline at 24 and 48 hours were analyzed using a one-sample t-test. A value of P ≤0.05 was considered statistically significant. Statistical calculations were performed using SPSS Statistics software v20 (IBM Inc).
5.3 Results

5.3.1 Patient Population, Feasibility and Safety

Fifty consecutive protocols were initiated over a span of 15 months. Over this period, the rate of admissions for AHF was 16.5 per month, of which 58% were eligible for treatment by the MSH La6 protocol. The mean age of the patients was 81 years; 56% were male (Table 4). The primary feasibility endpoint was reached in 36 patients (72%) who completed the protocol; of these, 19 continued protocol treatment for the full 48 hours and 17 completed the protocol early because target weight had been achieved at 24 hours. The mean duration that patients were treated within the Nomo-SDC was 33±15 hours.

The protocol was discontinued for 14 patients prior to completion or achievement of target weight. Seven of 14 were discontinued after alert notifications were reached. The protocol was discontinued in the remaining 7 patients for reasons unrelated to the Nomo-SDC, including patient non-compliance with medications and urine output measurements or extended ward absence for procedures.

During protocol treatment, there were no deaths and no transfers to an acute care setting. One patient was documented to have suffered a stroke. Safety markers for potassium homeostasis and changes in creatinine are also presented in Table 4. After initiation, there were no instances of severe hypokalemia. Hypokalemia occurred in 7% of patients at 24 hours and in 21% at 48 hours, requiring supplementation. Although 2 patients were withdrawn after meeting the alert notification for an increase in serum creatinine, no significant changes in serum creatinine were observed over the duration of the protocol. There were no instances in which serum creatinine increased >50% from baseline.

5.3.2 Adherence to Monitoring Actions
Opportunity-based scores for pre-specified monitoring actions were 100% (weights), 85% (urine output) and 88% (blood pressure). Similarly, scores for monitoring markers were 98% (serum sodium), 91% (potassium) and 95% (creatinine). The cohort opportunity score for combined clinical and biochemical monitoring was 91%. The median opportunity-based score per patient was 96% (IQR 87-100). The all-or-none score (patients receiving “perfect” monitoring) was 48%.

5.3.3 Adherence to Pre-specified Drug Administration

Between the 0-24 hour and 24-48 hour blocks, the mean IV furosemide dose administered increased significantly demonstrating dose titration was occurring within the protocol (Table 5). The cohort opportunity score for adherence to furosemide administration as prescribed by the Nomo-SDC was 92%. Per patient, the median opportunity-based score to complete up to 6 opportunities for furosemide administration during protocol treatment was 100% (IQR 88-100). The all-or-none score for furosemide administration as guided by the Nomo-SDC was 74%. Adherence to potassium replacement expressed as an opportunity score was 93% for hypokalemia and 71% for patients at risk of hypokalemia. The median opportunity-based score per patient to complete up to 5 opportunities for potassium replacement was 75% (IQR 50-100). The all-or-none score for potassium replacement as guided by the Nomo-SDC was 58%.

5.3.4 Treatment Effect

During the first 24 hours of the protocol, 90% of patients lost weight, with a median loss of 1.4kg (IQR 0.8-2.2). In the second 24 hours 73% of remaining patients lost a median of 0.8kg (IQR 0.4-1.2). Over the duration of protocol treatment, the median weight loss was 1.8kg.
(IQR 1.3-3.8). The median weight loss for the duration of hospital admission was 4.8kg (2.4-8.6).

Median length of stay for patients treated in the MSH La6 protocol was 7 days (5-16).
Table 4. Characteristics of the La6 Protocol Patients

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>N = 50</th>
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</thead>
<tbody>
<tr>
<td>Age, y (mean ± SD)</td>
<td>81 ± 12</td>
</tr>
<tr>
<td>Males</td>
<td>56%</td>
</tr>
<tr>
<td>HF as primary admitting diagnosis</td>
<td>94%</td>
</tr>
<tr>
<td>Previous diagnosis of HF</td>
<td>84%</td>
</tr>
<tr>
<td>Admission for HF exacerbation within the previous year</td>
<td>44%</td>
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<tr>
<td>History of Diabetes Mellitus</td>
<td>40%</td>
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<tr>
<td>History of Hypertension</td>
<td>74%</td>
</tr>
<tr>
<td>Medications at Home:</td>
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<tr>
<td>Loop Diuretic</td>
<td>86%</td>
</tr>
<tr>
<td>ACE Inhibitors/ARBs</td>
<td>48%</td>
</tr>
<tr>
<td>β-adrenergic Receptor Antagonists</td>
<td>72%</td>
</tr>
<tr>
<td>Systolic Blood Pressure, mmHg (mean ± SD)</td>
<td>127 ± 23</td>
</tr>
<tr>
<td>Heart Rate, bmin-1</td>
<td>84 ± 23</td>
</tr>
<tr>
<td>Respiratory Rate, min-1</td>
<td>21 ± 5</td>
</tr>
<tr>
<td>NT-proBNP, pg/ml</td>
<td>1091 ± 946</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>137 ± 5</td>
</tr>
</tbody>
</table>

**Serum potassium and creatinine at baseline and during protocol treatment**

Potassium at baseline, mmol/L (mean ± SD) | 4.3 ± 0.9 |
% severe hypokalemia (K<3.0mmol/L), (0h, 24h, 48h) | 4, 0, 0 |
% hypokalemia (K<3.5) | 34, 7, 21 |
% at risk of hypokalemia (< 4.0) | 58, 66, 47 |
% with hyperkalemia (>5.0) | 5, 4, 0 |
Creatinine at baseline, μmol/l (mg/dl) | 137 ± 60 (1.55 ± 0.68) |
Creatinine, % change from baseline, median (IQR) |
| 0-24 hours | 1.8 (-3.8 – 8.3) |
| 24-48 hours | 0 (-7.6 – 9.7) |
| 0 hours – end of protocol | 1.4 (-4.0 – 8.3) |

HF, heart failure; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; ACE, angiotension-converting enzyme; ARB, angiotension receptor blocker.
Table 5. Adherence to Furosemide and Potassium Administration as Guided by the Nomo-SDC

<table>
<thead>
<tr>
<th>Drug</th>
<th>0-24hrs</th>
<th>24-48hrs</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Furosemide (mg; Mean dose ± SD)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Planned</td>
<td>138 ± 54</td>
<td>220 ± 130*</td>
<td>261 ± 179</td>
</tr>
<tr>
<td>Given</td>
<td>138 ± 54</td>
<td>205 ± 130*</td>
<td>252 ± 173</td>
</tr>
</tbody>
</table>

Adherence to Nomo-SDC Furosemide Dosing

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Cohort opportunity score (%)</td>
<td></td>
<td>92</td>
</tr>
<tr>
<td>Per-patient opportunity score</td>
<td></td>
<td>100 (88-100)</td>
</tr>
<tr>
<td>median [IQR], %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-or-none score (%)</td>
<td></td>
<td>74</td>
</tr>
</tbody>
</table>

K Replacement (mEq; Mean dose ± SD)

<p>| | | | |</p>
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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Planned</td>
<td>71 ± 29</td>
<td>80 ± 42</td>
<td>102 ± 59</td>
</tr>
<tr>
<td>Given</td>
<td>63 ± 27</td>
<td>56 ± 41</td>
<td>81 ± 56</td>
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</table>

Adherence to Nomo-SDC Potassium Replacement Dosing

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<tbody>
<tr>
<td>Cohort opportunity score (%)</td>
<td></td>
<td>93</td>
</tr>
<tr>
<td>Hypokalemia</td>
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</tr>
<tr>
<td>Risk of hypokalemia</td>
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<td>71</td>
</tr>
<tr>
<td>Per-patient opportunity score</td>
<td></td>
<td>75 (50-100)</td>
</tr>
<tr>
<td>median [IQR], %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-or-none score (%)</td>
<td></td>
<td>58</td>
</tr>
</tbody>
</table>

*, p<0.05 vs. 0-24hrs.
5.4 Discussion

The goal for this quality improvement innovation was to optimize the efficiency of diuretic therapy for patients admitted with acute heart failure. After ensuring appropriate patient selection by the medical team, we demonstrated that it was feasible to empower a bedside caregiver group over an extended duration to assess efficacy, adjust diuresis and identify adverse effects, independent of physician reassessment unless pre-specified signs of intolerance or lack of effectiveness were identified. Our initial experiences suggest that this process was safe, resulted in excellent documentation of markers of quality care such as daily weights, and that clinical treatment targets could be achieved.

Like other standardized order sets (Group, 2009), the PPOS conveniently grouped medical orders decreasing variation in care and enhancing compliance with treatment guidelines. The PPOS was populated by information gleaned from routine medical consultation, identifying patients for whom diuresis was the central goal of therapy. The resultant treatment cohort was typical of community-based patients with AHF enrolled in registry studies, predominantly elderly with a moderate degree of renal insufficiency (Adams et al., 2005; Yeung et al., 2012). The algorithm for stepped diuretic care was based on procedures used in clinical trials (Bart et al., 2012; Felker et al., 2011) and deployed in a “real world” hospital ward setting, without mobilizing additional care provider resources per patient. The procedures required objective clinical measurements within the existing skill set of the nursing group, and did not mandate acquisition of new skills such as clinical volume assessment. An important consideration in design and safety of the Nomo-SDC was optimization of the human factor elements (Flin R, 2009) which may be reflected by adherence measures. When considering the uptake of all opportunities to perform monitoring activities, the high opportunity scores (>85%) suggested
that the Nomo-SDC directed process was well integrated into the workflow of the bedside RN and continued successfully over changes in shift personnel. Interestingly, this contrasted with poorer scores when adherence was evaluated by all-or-none methodology, likely owing to the multi-task process that constitutes evidence-based diuretic care. Other nomogram-driven therapies such as anticoagulation with intravenous unfractionated heparin (Cruickshank, Levine, Hirsh, Roberts, & Siguenza, 1991; Flaker, Bartolozzi, Davis, McCabe, & Cannon, 1994) may be simpler given one drug infusion to maintain a single laboratory measurement within a therapeutic range. Diuretic therapy for HF involves clinical and laboratory monitoring and an evolving therapeutic target over time. As such, all-or-none scoring, so-called “perfect care” could be compromised based on omission of single measurements.

Similar to monitoring actions, good adherence to the Nomo-SDC by the RN for furosemide administration and potassium supplementation for any hypokalemia was observed. The furosemide dosage increased during the 24-48 hour interval of the protocol, suggesting the initial dosage selection was conservative, supportive of the relative safety of the Nomo-SDC. Moreover, the design of the Nomo-SDC prompted dosage escalation every 12 hours if inadequate diuresis was noted by the point of care nurse. As such, efficiency may be enhanced compared to either fixed standing diuretic orders or awaiting daily assessment and prescription by the medical team. Every 12 hours, the Nomo-SDC also identified patients for selective reassessment by the medical team if prespecified safety endpoints, or insufficient efficacy targets were reached. These attributes of the MSH La6 Protocol contributed to safety, but equally avoided persistence with ineffective dosing. Adherence to the full dose of furosemide and potassium replacement prescribed by the Nomo-SDC was highest during the initial 24 hours, but tended to decline between 24-48 hours. Variability between individual patients likely increases
with respect to clinical status, goals of care and need for further therapy which may impede protocolized care over time and supports limiting the protocol duration to 48 hours..

This study has a number of limitations that merit acknowledgement. The number of patients included in this initial analysis is small and taken from a single center; however, the study cohort was representative of patients typically admitted with AHF to Mount Sinai Hospital and other academic and community centers. The MSH La6 Protocol is currently a paper based process and, for optimal monitoring of adherence and dissemination, adapting the tools to a computer order entry process would be an essential future direction. Automation would also likely reduce training requirements and may further improve uptake and adherence.

Our study also has strengths deserving of mention. The Mount Sinai La6 Protocol was designed with an interdisciplinary approach and appropriately pilot tested. Its design was based on the most recent and appropriate prior evidence. Analysis was performed on 50 consecutive patients, representing true uptake and adherence. In our institution, the MSH La6 Protocol impacted approximately one third of all admissions to HF. It is a process that could also be implemented by other care personnel such as physician assistants. Potential additional advantages to the Nomo-SDC included facilitated handover between shift RNs, with a graphical flow sheet of patient progress and an action plan for the subsequent 12-hour shift. A larger evaluation of markers of quality, efficacy and length of stay for patients treated by the MSH La6 Protocol compared to usual care is ongoing.
6 Linking Improved Processes Of Care With Timeliness Of Intravenous Diuresis For Acute Heart Failure

6.1 Introduction

The increasing prevalence of heart failure is reflected in the large population of patients experiencing episodes of decompensation and hospitalization for acute heart failure (AHF) (Yeung et al., 2012). Intravenous (IV) loop diuretic therapy is the current mainstay of in-hospital treatment (Heart Failure Society of et al., 2010; McKelvie et al., 2013; Yancy et al., 2013) for AHF. Efficient and effective treatment requires rational dose selection, as well as repeated actions to provide adequate monitoring of safety and evaluation of efficacy. The Canadian Cardiovascular Society, American Heart Association and the Heart Failure Society of America (Heart Failure Society of et al., 2010; McKelvie et al., 2013; Yancy et al., 2013) have published specific recommendations regarding appropriate monitoring of patients receiving IV loop diuretics in the setting of AHF. The quality of care indicators include, but are not limited to, daily measurements of serum potassium and creatinine, daily weights and fluid balance. Adherence to these recommendations is intended to reduce adverse events and, in the case of diuretic therapy, possibly improves the timeliness of appropriate dose adjustment and early efficacy of decongestion.

Accordingly, at our institution, a practice innovation was implemented to standardize and optimize the process of diuretic administration. Locally named the Mount Sinai Hospital (MSH) La6 Protocol, the objective of the process was to initiate effective diuresis within a 48-hour period after hospital admission. An algorithmic tool was designed to consolidate the actions required to monitor the effects of furosemide, and direct safe adjustment and administration of
multiple doses. The tool also delegated prescribing autonomy to the nurse at the point of care, with the intent of minimizing delays arising from frequent consultation between point of care medical staff and ordering physicians. The current analysis examines the impact of this quality improvement (QI) initiative on markers of quality heart failure (HF) care and rational diuretic prescription at our institution.
6.2 Methods

6.2.1 Setting

The QI initiative was conducted at MSH, an academic healthcare center in Toronto, Ontario, Canada. The MSH La6 Protocol consisted of 2 paper-based tools, the Physician Pre-Printed Order Set (PPOS) and the Nomogram for Stepped Diuretic Care (Nomo-SDC). These tools were developed during a 6-month process, beginning with a review of the literature and consensus building to assess needs and objectives. The protocol was then drafted and revised by a multi-disciplinary panel including cardiology, hospital pharmacy, nursing administration and nursing education. At our institution, practice changes are reviewed by the Clinical Practice Committee, the Joint Health and Safety Committee, Risk Management, and Health Records, with final approval by the Medical Advisory Committee. Data collection was approved by the MSH Research Ethics Board.

6.2.2 Quality Improvement Interventions

The first tool employed after initial evaluation of the patient was the Physician Pre-Printed Order Set (PPOS). This tool was completed by the treating physician and met several objectives. The first objective of the PPOS was to guide selection of appropriate AHF patients for whom the primary treatment goal was relief of fluid congestion associated with AHF. The target population for this QI project was chronic heart failure patients with previous use of oral loop diuretics admitted to a hospital ward setting. A checklist was provided to specify inclusion and exclusion criteria. Inclusion checkbox criteria were: 1) a mandatory previous diagnosis of HF and home dose of oral furosemide, 2) an elevated jugular venous pressure (JVP), 3) evidence of pulmonary or peripheral edema, 4) ascites, 5) ≥2 kilograms of weight to lose by physician estimate, and 6) a serum NT-pro BNP >135pmol/L (Maisel et al., 2002; McKelvie et al., 2013).
Patients were deemed eligible if they met the mandatory criteria (checkbox 1) as well as at least one checkbox 2 to 6. Exclusion checkboxes were also listed to prevent use of the protocol in patients who would have been excluded from clinical trials of multi-dose furosemide administration (Bart et al., 2012; Felker et al., 2011). Exclusion checkbox criteria were: 1) patients with a new diagnosis of heart failure on admission and 2) furosemide naïve (not taking oral furosemide at home), 3) systolic blood pressure of less than 90 mmHg and 4) a serum creatinine greater than 260 micromol/L.

The second objective of the PPOS was to standardize initial twice-daily bolus furosemide prescription, to standardize monitoring procedures and to specify a target weight loss to be met after 48 hours. The third objective of the PPOS was to have the treating physician provide conditional orders that enabled scheduled diuretic therapy to proceed without further physician consultation. The PPOS also compelled the treating physician to provide standardized conditional orders that automatically suspended the protocol and mandate notification of the physician team for reassessment based on changes in systolic blood pressure, electrolyte abnormalities, changes in serum creatinine and failure to meet weight loss targets.

The second tool employed was the nomogram for stepped diuretic care (Nomo-SDC) implemented by the caregiver at the bedside. The Nomo-SDC employed an evidence-based algorithm for twice daily assessment and selection of furosemide dosing as well as monitoring of serum biochemistry and prescription of potassium replacement. Patient reassessment within the Nomo-SDC was coordinated with a standard 12 hour nursing shift for minimal disruption of workflow. Markers of efficacy and safety were collated within the Nomo-SDC, and population of the algorithm tool then led to selection of the next dose of furosemide, without requiring additional reassessment by the medical team.
Implementation of the QI project included preparation of education packages including oral, visual, and written materials and focused sessions were conducted with all active nursing staff on two hospital wards, as well as attending medical staff and residents. On medical floors, weight scales were inventoried, calibrated and procedures to ensure daily access to the same scale for all ambulatory and semi-ambulatory inpatients. Education also required RNs to perform a mock run through of the nomogram, populating each step and following through to the next. Two hospital pharmacist, thoroughly educated on the MSH La6 Protocol were also available to support medical and nursing staff. The decision to use the protocol was left at the discretion of the attending physician. There were no additional clinical resources and no changes in nurse to patient ratio required to complete this initiative.

6.2.3 Evaluation

We performed a pre and post-implementation observational study of this QI initiative following an implementation period. Data on demographics, home medications, serum sodium, serum potassium, serum creatinine, and all recorded weights, if available, were collected from the initial 48 hour period of admission and the length of stay was recorded for all patients included in this analysis.

The pre-implementation cohort was assembled using the electronic patient record system (Cerner Powerchart) to retrospectively identify consecutive patients admitted with a primary diagnosis of AHF over a 32-month period prior to the implementation of the MSH La6 Protocol between March 3rd, 2010 and October 24th, 2012. Patients with a primary diagnosis of AHF during admission to MSH who had received at least one dose of bolus intravenous (IV) furosemide within 24 hours of admission were included. Patients who received a continuous
infusion of furosemide within the first 48 hours of admission to hospital and/or those who did not received at least one dose of bolus IV furosemide within 24 hours of admission were excluded.

The post-implementation cohort was collected prospectively and consisted of all consecutive patients admitted to MSH with the primary diagnosis of AHF over 8 months between July 1\textsuperscript{st}, 2013 and February 27\textsuperscript{th}, 2014. The same inclusion and exclusion criteria used for the pre-implementation were also used to select the post-implementation cohort, regardless of use of the La6 Protocol and therefore included patients who were treated using the protocol, and patients who received routine care.

The entire populations from both the pre- and post-implementation cohorts were also evaluated as eligible or ineligible for treatment by the MSH La6 protocol, based on the inclusion and exclusion criteria specified in the PPOS. Finally, consecutive patients treated using the La6 Protocol between December 15th, 2012 to June 30th, 2013 formed the implementation cohort.

6.2.4 Process and outcome measures

The primary process measure was adherence to daily monitoring of patients receiving IV loop diuretics as currently recommended by major cardiovascular societies. In our QI program, monitoring measures included daily serum potassium, daily serum creatinine and daily ward weight. Compliance to these best practices measures was determined using two methodologies. Firstly, a composite opportunity-based score was determined for both cohorts. The score was calculated as the total number of monitoring measures completed divided by the total number of actions required (3 daily measurements; baseline, 24 and 48 hours). Patient level care was evaluated by deriving an all-or-none score (or a “defect-free score”), defined as the proportion of patients having all of the pre-specified monitoring markers measured for which they are eligible (T. Nolan & Berwick, 2006; Peterson et al., 2010). Thus, this score reflected the proportion of
patients receiving ‘perfect’ care. Additionally, the proportion of patients with a minimum of 2 ward weights recorded during the 48-hour period was calculated as a minimum pre-requisite measure that demonstrated diuretic progress was being monitored. All process measures were also expressed as group means calculated each consecutive month throughout the pre- and post-implementation time periods for the purpose of constructing process control charts.

Outcome measurements were selected to demonstrate evidence of rational diuretic prescription and dose adjustment in the first 48 hours. Total furosemide doses administered were recorded in the 0-24 hour block, 24-48 hour block and 0-48 hours. The proportion of patients who had an increase in furosemide dose in the second 24-hour block was determined. Other outcome measurements included change in weight over 48 hours and length of stay.

Safety was examined in multiple ways. Deaths or transfers to a higher acuity setting during use of the protocol were recorded. Abnormalities of serum biochemistry were examined over the 0-24h and 24-48h time periods during the first 48 hours of admission for all cohorts. Hypokalemia was considered an adverse effect of diuretic therapy and was classified as: severe hypokalemia (serum K\(^+\) <3.0mmol/L, considered a serious adverse event) and hypokalemia (Gennari, 1998) (serum K\(^+\) ≥3.0 and <3.5mmol/L). Since potassium replacement was included in the Nomo-SDC, hyperkalemia (serum K\(^+\) >5.0 mmol/L) was also considered a serious adverse event. A rise in serum creatinine >50% above baseline at anytime was considered a serious adverse event, based on the RIFLE criteria (Bellomo et al., 2004; Zhang et al., 2015) for acute kidney injury (AKI).

### 6.2.5 Data analysis

Data are presented as mean ± standard deviation or median and interquartile range, as appropriate. Normality was assessed using the Kolmogorov-Smirnov test. Between group
differences in baseline characteristics and safety markers were compared using the Mann-Whitney U test or chi squared analysis for continuous and categorical variables, respectively. Similarly, differences in furosemide doses between cohorts were compared using Mann-Whitney U tests. Within group differences in furosemide doses between consecutive 24-hour time intervals were compared using Friedman’s test. A value of $P \leq 0.05$ was considered statistically significant for all tests. Statistical calculations were performed using SPSS Statistics software v20 (IBM Inc).

As noted, group means for process measure scores were calculated on a monthly basis for the entire pre- and post- implementation cohorts. Statistical process control charts, also known as Shewhart control charts, were used to determine if these process measures of heart failure care changed over time during the 32 months pre-implementation of our QI initiative and for 8 months after. Charts were displayed with time on the x-axis, and on the y-axis the measurement in question and 3 additional lines (Benneyan et al., 2003; Mohammed et al., 2008). The central line indicated mean and 2 additional lines demonstrated the upper and lower control limits, 3 standard deviations (SDs) away from the mean. If all data points were contained within the control limits, the process was considered to be stable, displaying common stable variation. If a data point or multiple data points fell outside of control limits, Shewhart rules were used to look for special causes of variation. Eight consecutive data points showing evidence of unstable variation represented a sustained change in the process and a new mean central line was calculated. Shewhart control charts were created using CHARTrunner Lean v3.0 (PQ Systems Inc).
6.3 Results

6.3.1 Cohorts

The pre-implementation cohort was comprised of 338 patients (Figure 4). Of these, 177 would have been eligible for the La6 Protocol. The first use of the La6 Protocol for treatment of AHF occurred on December 15th, 2012. During the implementation period, 9 patients were treated using the La6 Protocol. The post-implementation cohort consisted of 121 patients. Of these, 71 patients were eligible for treatment using the La6 Protocol, 38 of whom were treated using the protocol (ON). Of the total post-implementation cohort, 83 patients were treated by usual-care practices (OFF) at our institution. Baseline characteristics for the pre-, post- and implementation cohorts are presented in Table 6. There were small differences between the pre and post implementation cohorts. Compared to the pre-implementation cohort, the post-implementation cohort was slightly older with an equal distribution of men and women.

During protocol treatment, there were no deaths and no transfers to an acute care setting. Safety markers for potassium homeostasis and changes in creatinine are also presented in Table 6. There was no significant difference between the pre- and post-implementation cohorts in serum potassium and creatinine measurements on admission to hospital. Similarly, there was so significant difference in incidence of severe hypokalemia, hypokalemia, or percent change in serum creatinine from baseline between the two groups. Incidence of hyperkalemia was significantly higher in the post-implementation cohort at 5% compared to 0.6% in the pre-implementation cohort in the 24-48 hour time period.

6.3.2 Process measures

Shewhart control charts demonstrated significant improvement in adherence to best practices for monitoring the safety and efficacy of diuresis. Between the pre and post
implementation period, a significant improvement was observed in the opportunity-based composite score from a mean of 82% to 90% and the all-or-none score from 30% to 57% (Figures 5A and 1B). The post-implementation improvement appeared stable. Similarly, the proportion of patients who had a minimum of 2 weight measurements recorded within 48 hours of admission to hospital also increased significantly from 45% to 81% (Figure 5C).

6.3.3 Furosemide Prescription Pre- and Post-Implementation

Total furosemide doses administered over 48 hours in the pre and post implementation cohorts are summarized in Table 6. The median furosemide doses given in the first and second 24-hour blocks were similar between the pre and post implementation cohorts. Within the pre-implementation cohort, the mean furosemide dose significantly decreased between the 0-24 and 24-48h time block, while no significant change was observed within the post-implementation cohort.

6.3.4 Impact of the La6 Protocol

To examine the impact of the MSH La6 Protocol on furosemide administration in more detail, we evaluated only patients who were eligible for treatment within the protocol (Table 7). Compared to the pre-implementation cohort, the mean furosemide dose was significantly higher in the 24-48 hour time block in the post implementation eligible patients. Among the post implementation eligible cohort, furosemide doses in the 24-48 hour block and over the entire 48 hours were higher in patients treated ON protocol compared to OFF. Considering all patients treated ON protocol in the implementation and the post-implementation cohorts, compared to the first 24 hours, furosemide doses increased significantly in the second 24 hours.

As noted in the process measures, only 45% of the pre-implementation cohort had a minimum of 2 weights to evaluate response to diuretic treatment. Of those, 70% had a
documented weight loss of $1.8 \pm 1.7$ kg. In the post implementation cohort, a significantly higher proportion of patients, 86%, had a minimum of 2 weights and the mean change in weight was $1.9 \pm 1.6$ kg. The proportion of patients treated ON protocol with at least 2 weight measurements was 89%, with 94% demonstrating weight loss. The mean weight loss in the ON protocol group was $2.3 \pm 1.6$ kg. For comparison, the implementation cohort of patients, consisting of 47 patients treated ON protocol, had a mean weight loss of $2.2 \pm 1.8$ kg, with 93% demonstrating weight loss. The median length of stay did not change between the pre and post-implementation periods.
Table 6. Clinical Characteristics of the Pre-, Post- and Implementation Patient Cohorts

<table>
<thead>
<tr>
<th></th>
<th>PRE N = 338</th>
<th>POST N = 121</th>
<th>p-value</th>
<th>Total ON N=47</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y [median (IQR)]</td>
<td>81 (72 - 88)</td>
<td>84 (77 - 89)</td>
<td>0.01</td>
<td>81 ± 12</td>
</tr>
<tr>
<td>Males</td>
<td>46%</td>
<td>47%</td>
<td>0.21</td>
<td>55%</td>
</tr>
<tr>
<td>Medications at Home:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop Diuretic</td>
<td>55%</td>
<td>66%</td>
<td>0.04</td>
<td>85%</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>9%</td>
<td>7%</td>
<td>0.58</td>
<td>2%</td>
</tr>
<tr>
<td>Spironolactone/Eplerenone</td>
<td>11%</td>
<td>10%</td>
<td>0.86</td>
<td>11%</td>
</tr>
<tr>
<td>ACE Inhibitors/ARBs</td>
<td>37%</td>
<td>49%</td>
<td>0.03</td>
<td>49%</td>
</tr>
<tr>
<td>β-adrenergic Receptor Antagonists</td>
<td>45%</td>
<td>60%</td>
<td>0.01</td>
<td>70%</td>
</tr>
<tr>
<td>Digoxin</td>
<td>11%</td>
<td>15%</td>
<td>0.26</td>
<td>26%</td>
</tr>
<tr>
<td>Ca 2+ channel blocker</td>
<td>23%</td>
<td>36%</td>
<td>0.01</td>
<td>28%</td>
</tr>
<tr>
<td>Total Furosemide Dose (mg; Mean dose ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 -24 hours</td>
<td>94 ± 62</td>
<td>99 ± 63</td>
<td>0.40</td>
<td>121 ± 62</td>
</tr>
<tr>
<td>24 – 48 hours</td>
<td>87 ± 56*</td>
<td>103 ± 70</td>
<td>0.11</td>
<td>132 ± 73</td>
</tr>
<tr>
<td>Total: 0 – 48 hours</td>
<td>159 ± 109</td>
<td>173 ± 122</td>
<td>0.39</td>
<td>237 ± 117</td>
</tr>
<tr>
<td>Safety Markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium at baseline, mmol/L [median (IQR)]</td>
<td>4.2 (3.9 - 4.6)</td>
<td>4.2 (3.8 - 4.6)</td>
<td>0.48</td>
<td>4.3 ± 0.9</td>
</tr>
<tr>
<td>% severe hypokalemia (K&lt;3.0mmol/L), at 24h, 48h</td>
<td>4, 2</td>
<td>5, 0</td>
<td>0.57, 0.21</td>
<td>7, 0</td>
</tr>
<tr>
<td>% hypokalemia (K&lt;3.5)</td>
<td>17, 20</td>
<td>23, 14</td>
<td>0.29, 0.16</td>
<td>31, 7</td>
</tr>
<tr>
<td>% hyperkalemia (&gt;5.0)</td>
<td>2, 0.6</td>
<td>2, 5</td>
<td>1, 0.01</td>
<td>2, 4</td>
</tr>
<tr>
<td>Time Period</td>
<td>Creatinine at baseline, μmol/l (mg/dl)</td>
<td>Creatinine, % change from baseline, median (IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------------------------</td>
<td>--------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-24 hours</td>
<td>104 (77 – 145)</td>
<td>-1.1 (-5.4 – 7.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>108 (79 – 143)</td>
<td>1.6 (-3.4 – 6.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.19 (0.19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 (-2.9 – 4.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-48 hours</td>
<td>0.68</td>
<td>2.1 (-3.3 – 9.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.6 (-3.1 – 13.2)</td>
<td>0.16 (0.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.4 (-3.3 – 9.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-48 hours</td>
<td>0.19</td>
<td>2.7 (-6.1 – 14.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.6 (-2.7 – 19.4)</td>
<td>0.13 (0.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.0 (-4.0 – 13.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*, sig difference in furosemide dose between 0-24 hours and 24-48 hours within the same cohort.
ON protocol (n=47) cohort presented for visually comparative purposes.
Table 7. Furosemide Dose Adjustment in Patients Eligible for the MSH La6 Protocol

<table>
<thead>
<tr>
<th>Time period from admission</th>
<th>Overall Eligible</th>
<th>Post Implementation</th>
<th>Implementation + post-implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRE N=177</td>
<td>POST N=71</td>
<td>p-value</td>
</tr>
<tr>
<td>0 -24 hours</td>
<td>103 ± 63</td>
<td>115 ± 68</td>
<td>0.20</td>
</tr>
<tr>
<td>24 – 48 hours</td>
<td>98 ± 60</td>
<td>122 ± 73</td>
<td>0.03</td>
</tr>
<tr>
<td>0 – 48 hours</td>
<td>179 ± 116</td>
<td>210 ± 129</td>
<td>0.08</td>
</tr>
<tr>
<td>% of patients with an increase in dosage</td>
<td>17%</td>
<td>27%</td>
<td>0.08</td>
</tr>
<tr>
<td>% of patients demonstrating weight loss</td>
<td>70%</td>
<td>86%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*, sig difference in furosemide doses within groups between 0-24 hours and 24-48 hours. ON protocol (n=47) cohort presented for visually comparative purposes.
Figure 4. Analysis Cohorts

Each cohort was divided into patients eligible for the protocol and those who were not. The post-implementation cohort was further divided into patients treated using the protocol and those treated with usual (routine) care. The implementation period was comprised of 9 patients treated on the protocol and was not included in the final pre- and post-implementation impact analysis.
5A. Opportunity-Based Score for Monitoring of Daily Serum Potassium, Serum Creatinine and Weight

Cohort Opportunity-Based Score change between the pre and post-implementation periods. The process was deemed stable prior to and post implementation of the La6 Protocol in July of 2013, with a significant improvement from 82% to 90%. Eight data points of collection post-implementation signal sustained change. Implementation period between November 2012 and June 2013 removed.
5B. All-or-None Score for Monitoring of Daily Serum Potassium, Serum Creatinine and Weight

Cohort All-Or-None Score change between the pre and post-implementation periods. Eight data points of collection post-implementation signal sustained change, with a significant improvement from 30% to 57%. Implementation period between November 2012 and June 2013 removed.
5C. Proportion of Patients With At Least 2 Weight Measurements in 48 Hours

The mean proportion of patients with a minimum of 2 weight measurements recorded in the first 48 hours of admission improved significantly from 45% pre-implementation to 81% after the implementation of the La6 protocol in July of 2013. The process was deemed stable in both periods, and the change sustained. Implementation period between November 2012 and June 2013 removed.
6.4 Discussion

Recent studies have provided clinicians with data to inform rational selection of diuretic therapy for acute heart failure as well as an improved understanding of expected efficacy of treatment, side effects and requirements for monitoring (Bart et al., 2012; Felker et al., 2011). At our institution, such knowledge was incorporated into practice by implementing a tool that promoted rational IV furosemide dose selection and subsequent adjustment. Use of these tools additionally improved adherence to monitoring guidelines, with the goal of ensuring that diuresis remained safe at the same time as effective. Another objective of our QI initiative was to improve the timeliness of diuretic therapy by empowering bedside personnel, the registered nurse at our institution, to identify adverse events and adjust diuretic dosing according to an evidence-based algorithm, without delays to consult the medical team. Our results demonstrated the impact of the intervention to improve documentation of markers of quality care such as daily weights, and serum biochemistry. Moreover, the intervention appeared to reverse a pattern of decline in diuretic dosing after the first hospital day, and this practice appeared safe despite delivery of a higher total dose of furosemide. A higher proportion of patients both in the post-implementation phase and further treated with the La6 Protocol appeared to lose weight over the initial 48 hours. These findings were consistent with the hypothesis that implementation of this practice change resulted in improved early efficacy of diuretic therapy due to timelier dose adjustment.

The patient population evaluated was typical of published registry experience (Adams et al., 2005; Yeung et al., 2012), clearly older than patients enrolled in clinical trials, with a higher proportion of women. Importantly, the pre-implementation cohort demonstrated relative stability in quality of care and was collected after the publication of significant clinical trials (Bart et al.,
2012; Felker et al., 2011) that may have affected diuretic practices. In the post-implementation cohort, the proportion of patients admitted with AHF who were eligible for treatment by the La6 Protocol was similar to the pre-implementation cohort at approximately 50%. The use of the La6 Protocol was not mandated and uptake amongst eligible patients was not complete. The explanations for incomplete uptake were not clear. However, the La6 Protocol required adoption of a practice change by both attending medical teams as well as nursing and resistance to change may not therefore be surprising. Even without full uptake of the practice change, medical staff was exposed to the education regarding best practices for administering diuretics, offered during implementation of the La6 Protocol. This may have contributed to the sustained improvement with respect to processes of care that we observed in the post-implementation period, particularly optimal monitoring of patients.

In the evaluation of this QI initiative, we considered process measures as specific steps that can drive improvement of a valuable outcome. We observed that better monitoring of patients receiving IV loop diuretics in the post-implementation period was associated with evidence of improved timeliness of therapy and improved early efficacy. Several observations of patterns of furosemide prescription suggested timelier dose adjustment in the second 24 hours after admission. In the pre-implementation period, total furosemide dose actually decreased significantly which was demonstrated using data from the drug administration record of the electronic patient chart. It is unlikely that furosemide doses were systematically reordered in smaller amounts on the second day of admission. However, delays in furosemide reassessment and reordering may have contributed to a longer interval between doses administered and a net decrease in total dose over a 24-hour period. In the post-implementation period, this trend was reversed as no decline in furosemide dosing was observed in the 24-48 hour period. Importantly,
this occurred with no increase in hypokalemia or adverse changes in serum renal function, possibly attributed to improved adherence to monitoring and systematic practices for potassium replacement.

As noted, evidence of a sustained change in practice was observed in the post-implementation period whether the La6 Protocol was engaged or not. However, we observed further impact when the protocol was engaged. A principle of the protocol design was to link actions for monitoring to actions that optimized efficacy of diuresis, allowing safe titration of the diuretic dosage by a single care-giver group, the RN. Indeed in the post-implementation period, the proportion of patients for which an increase in diuretic dosage was observed and the proportion of patients with recorded weight loss over the initial 2 days of hospitalization were highest in patients treated with the La6 protocol. Our observations also demonstrated the need to implement directive processes to translate new knowledge into clinical practice. In the pre-implementation period, we observed processes of clinical care appeared stable with obvious opportunities for improvement even though the DOSE study (Felker et al., 2011) had been published prior. After rollout of the La6 Protocol we observed the largest impact on patterns of furosemide prescription in patients treated on the La6 Protocol. This supported an assumption made during formulation of the protocol, that administration of loop diuretics can be an empiric practice based on variable experiences of ordering physicians.

The specific change in practice delegated clinical and prescriptive activity to a non-physician point-of-care group over an extended duration of time. Although algorithms for stepped diuretic care have been employed within clinical trials (Bart et al., 2012; Felker et al., 2011), this intervention occurred in a real world setting, a standard hospital ward, without mobilizing additional care provider resources per patient. Progress in the protocol was informed
by objective clinical measurements that were within the existing skill set of the RN group, and did not mandate acquisition of new skills such as clinical volume assessment. The process would also be applicable to other personnel with continuous presence of hospital wards such as physician assistants.

Limitations to our reported experience included the fact that the MSH La6 protocol was an initiative undertaken and evaluated at a single Canadian center and can not be generalized to other hospital settings. We were unable to examine actual patient weight loss in the first 48 hours after admission in the pre-implementation cohort due to insufficient numbers of weight measurements. It is possible then that diuretic efficacy with respect to weight and fluid loss in the pre-implementation cohort was actually comparable to the post-implementation cohort, despite poorer process measure scores. However, this supports our contention that adherence to best practices with respect to monitoring is essential to proper evaluation of diuretic therapy in clinical practice. We did not observe an impact of our intervention on length of stay over 8 months, possibly because there was insufficient uptake of the protocol for eligible patients. The MSH La6 Protocol is currently a paper based process and, for optimal monitoring of adherence and dissemination, adapting the tools to a computer order entry process would be an essential future direction. Automation may further improve uptake and adherence.

In conclusion, a quality improvement initiative to improve and standardize processes of care for IV diuresis was undertaken. Our experience demonstrated that higher adherence to practices for monitoring was not more time-consuming, and was instead linked to evidence of better timeliness of care.
7 General Discussion

Principles of quality improvement in healthcare were employed in the design, implementation and evaluation of a clinical tool to provide standardized evidence-based, safe and timely loop diuretic therapy for patients admitted to hospital with acute heart failure. An important strategy to improve timeliness used in the process was empowerment of the bedside caregiver to autonomously assess efficacy markers of diuresis, appropriately adjust dosing and identify adverse events for 48 hours after initial clinical assessment at the time of admission.

The objectives of this quality improvement innovation were to impact the safety and timeliness of decongestion for heart failure. The hypothesis of this project was that safety and timely administration of diuretics would improve after employing strategies to enforce guideline-directed patient monitoring, enforce evidence-based rational selection and administration of diuretics and, bypassing barriers to interprofessional communication. The evaluation demonstrated several findings in support of our objectives and hypotheses: 1) The pre and post implementation cohorts, including patients treated within the La6 Protocol, were representative of community-based patients with acute heart failure enrolled in registry studies, elderly with a moderate degree of renal insufficiency, 2) Adherence to the monitoring tasks, furosemide administration and potassium replacement was measured and shown to be excellent, supporting feasibility of the process, 3) Excellent adherence to the protocol appeared to translate to improvement in guideline-directed patient monitoring compared to the pre-implementation period, 4) With respect to safety, no increase in incidence of adverse events was detected, despite improved surveillance of patients, 5) In the pre-implementation period, a significant decline in furosemide doses was observed between the first 24 hours of admission and the second 24 hours, a trend that was clearly reversed in the post-implementation cohort. Reversal of this trend was
most evident when the La6 Protocol was employed, supporting the contention that the process enhanced timeliness of furosemide administration, and 6) No impact on length of stay was noted in the post-implementation period.

The Canadian Society of Hospital Pharmacists defines an order set ‘as a predetermined, evidence-based prescribing tool to help physicians and other healthcare professionals to effectively and efficiently implement best practices.’ ("How to Promote Best Practice and Safety through the Use of Order Sets. From Paper to Practice: Incorporating Evidence Into Your Pharmacy Practice. CSHP 2015 Toolkit.," 2015) Algorithmic tools and standardized order sets are common in clinical care (Cruickshank e t al., 1991; Goldberg et al., 2004; Raschke, Reilly, Guidry, Fontana, & Srinivas, 1993). Multiple systematic reviews have concluded that the use of order sets leads to an improvement in guideline adherence, treatment outcomes, and processes of care, efficiency and cost (Chan et al., 2012; Group, 2009). Order sets can be divided into those that aid diagnosis and treatment. The MSH La6 Protocol was innovative in designing a combined tool that both aided the medical team in proper diagnosis of congestion in the setting of AHF as well as served as a prescription and monitoring tool for the beside RN. Specifically, the Pre-Printed Physician Order Set (PPOS) grouped medical orders, providing the rationale necessary to understand current guideline recommendations and therefore decrease variation in orders and the Nomo-SDC prescribed and adjusted furosemide dosing administered by the ward RN. In comparison to other order sets that have a single preset clinical endpoint, the Nomo-SDC design was novel as a treatment algorithm in having adaptable drug dosages and endpoints that changed according to the monitoring completed by the responsible nurse. In this way, the appropriate treatment depended on careful and complete monitoring of the patient.
It was hypothesized that timeliness would be favourably impacted by the strategy to empower bedside caregivers, the ward RN, to enable therapy with minimal delays for consultation with the physician team. The clinical assessment and dose adjustment performed by the bedside RN were within their current skill set and did not require additional training, beyond understanding the algorithm itself. The design of the protocol took into account integration into nursing shift workflow and served as a graphical hand-over tool between nursing staff. The high opportunity scores suggested that adherence to the La6 Protocol by RNs was feasible.

Evaluating timeliness in a quality improvement intervention involves, firstly, identifying and defining measures related to timeliness. Timeliness is evaluated directly through time measurements, including time to treatment, waiting times, or events within a specific time period. Therefore timeliness was assessed in this project by measuring events relating to furosemide treatment within a specified time period after admission to hospital, which would also take into account time to treatment. Markers of timeliness measured included furosemide dosages administered in each 24-hour block as well as weight loss achieved. The pre- and post-implementation analysis suggested that timeliness of diuretic therapy was in fact improved. The intervention appeared to reverse a decline in furosemide dosing after the first hospital day, and with a higher total dose of furosemide administered in the first 48 hours. In the pre-implementation period, there was a significant decrease in the total dose of furosemide received in the second 24-hour block. It seems unlikely that reordering smaller doses of furosemide on the second day of admission was intentional. Instead, delays in furosemide reassessment and reordering may have led to a longer interval between doses administered and a net decrease in total dose over a 24-hour period. In the post-implementation period, this trend was reversed as no decline in furosemide dosing was observed in the 24-48 hour period. No increase in the
incidence of adverse events were observed with these results, possibly attributed to the improved adherence to monitoring and systematic practices for potassium replacement observed.

The greatest impact on the behavior of diuretic administration in the post-implementation cohort was observed in patients treated using the La6 protocol. The increase in diuretic dosage and the proportion of patients with recorded weight loss over 48 hours was highest in these patients. These findings were supportive of the hypothesis that implementation of this practice change resulted in the improvement of timely dose adjustment and consequent early efficacy of therapy. The design of the protocol supported systematic up-titration of the furosemide dose based on markers of diuretic progress or lack thereof. By contrast, the DOSE trial derived a rational dosing regimen that was fixed for the initial 48 hours prior to reassessment by the treating physician (Felker et al., 2011). The La6 Protocol is similar to CARRESS-HF trial in a more active adjustment of diuretics (Bart et al., 2012).

We observed an association between improved adherence to monitoring processes and the outcome of apparent improvement in timeliness of diuretic administration. In the pre-implementation cohort, it was not possible to meaningfully examine weight loss in the first 48 hours after admission due to insufficient numbers of weight measurements. This was observed at the same time a decline in dosage was observed between the first and the second 24 hours. The experience of the post-implementation cohort suggests it is possible that a simple intervention to improve adherence to monitoring alone, may confer several benefits to diuretic care. Monitoring actions demonstrate the progress or lack of progress in decongestion and likely actively drive the adjustment of dosages, and thus timeliness of treatment, even in the absence of the titration algorithm for diuretics. Detection of adverse events is important, but appropriate monitoring also facilitates safe up-titration of diuretics. In the current era, there is a growing movement to
compel reporting of metrics that indicate good quality of care. Without sufficient monitoring
data, neither adequacy nor deficiency of care can be measured appropriately.

A significant limitation in fully understanding the potential impact of this quality
improvement intervention was the incomplete uptake of the La6 Protocol in eligible patients.
This challenge has been reported by multiple studies evaluating adoption of new order sets
(O'Connor, Adhikari, DeCaire, & Friedrich, 2009; Sano, Waddell, Solimando, Doulaveris, &
Myhand, 2005). Despite evidence, in this study as well as other quality improvement projects,
showing that unfavorable variation in drug prescription can lead to poorer patient outcomes,
resistance to change in clinical practice is commonplace among medical staff (Group, 2009).
One possible reason for incomplete uptake is the structure of the CTU at an academic institution
(previously discussed in Section 2.1.1), in which there is a constant rotation of trainees in
medicine through different specialties. This can potentially lead to suboptimal awareness of a
new tool or protocol, despite best efforts for ongoing education. Another possible hindrance to
uptake is the paper format of the protocol. Adaptation into computer based order form entry
could lead to improved uptake. Suboptimal uptake may have contributed to the null result with
respect to length of stay in hospital. Effect on length of stay may be possible with wider
dissemination of the intervention to other institutions as has been shown in other studies
(Fishbane et al., 2007). Despite incomplete uptake of the La6 protocol itself, whether treated on
or off the protocol, sustained improvement with respect to processes of care were observed in the
post-implementation cohort particularly optimal monitoring of patients. Education regarding
evidence on diuretic therapy and proper monitoring, provided to all medical and nursing staff,
may have contributed to this change.
Limitations of the study design of this quality improvement intervention also merit discussion. A pre-and-post design was used for evaluation between the pre-cohort, which was studied retrospectively, and the post cohort, studied prospectively. Improvement in monitoring adherence was tested using a time series design. This design is beneficial in evaluating whether an intervention has an effect on a system while still considering the underlying stable trend that exists within the system (Cook TD, 1979; Eccles, Grimshaw, Campbell, & Ramsay, 2003). In this way, a significant change in practice can be attributed to the intervention with more confidence because a system is evaluated for stability before and after the implementation of the intervention. This type of design was considered a better option to a patient randomized controlled trial within one institution, in which it would have been difficult to maintain a control group that was not contaminated by the intervention and education of the medical staff. However, a pre and post design or comparison to a historic control has a few recognized limitations. Although this type of study is considered superior to simple observational studies, there is a risk of over estimating the effect of the quality intervention (Lipsey & Wilson, 1993). Alternatively, a cluster-randomized trial can be used for this type of evaluation and may be considered the best option for quality evaluation (Klar & Donner, 2001; D. M. Murray, Varnell, & Blitstein, 2004; Parry & Power, 2016). Clusters would be formed at a hospital level, with some acting as controls and others implementing the intervention. Data would then be collected on a patient level and impact of the intervention evaluated. Having too few clusters for randomization can create bias and a statistical imbalance therefore sample cluster size for randomization needs to be inflated to increase statistical efficiency (Eccles et al., 2003). As such, the decision was made to test the MSH La6 Protocol on an institutional level for safety and adherence prior to application at multiple centers in a randomized design.
8 Conclusions and Future Directions

In conclusion, the MSH La6 Protocol was developed to improve the safety and timeliness of IV furosemide administration in the first 48 hours of admission to hospital in patients with AHF. Evaluation demonstrated that the practice change was safe in both adherence to nomogram steps and no increased incidence of adverse events in comparison with routine practice. Timeliness of diuretic administration was improved through rational dose selection and adjustment by the bedside RN as well as streamlined communication between medical and nursing personnel.

The implications of these findings can be interpreted in context of 3 structural levels of the healthcare system. Firstly, the micro level refers to the patient and the clinical team. The MSH La6 Protocol was developed with the goal of improving patient care on an individual level. In addition to whole cohort measurements and improvement evaluation, assessment also included patient level adherence. Care process markers were measured and scores calculated on a per-patient level. Results demonstrated good adherence to monitoring and safety for each individual patient placed on the protocol. Pre- and post-implementation evaluation also showed significant improvements in patient monitoring as recommended by guidelines. This demonstrated the significance of patient care processes to the safety of hospital care in each patient’s management plan. Developing the Nomo-SDC to be evidence-based was also an integral part of ensuring that patient care was up to best standards. Improvement in patient care processes is also crucial to patient health outcomes. Thus, impacting the micro system of patient care, the MSH La6 Protocol has important implications on patient health outcomes as well.

Next the protocol had implications on a meso level, which is defined as impact of a quality improvement initiative analyzed on an organizational or community level, in this case the
entire institution. This project set out to appropriately standardize care of patients on IV diuretic therapy. Evaluation of institutional practices revealed significant variation in furosemide dose selection in AHF patients. The same evaluation revealed similar substantial variation in dose adjustment in the first 48 hours of admission to hospital. This variation was hypothesized to lead to ineffective dosing and consequent delays in therapy and hospital stay. The implementation of this protocol, more specifically the Pre-Printed Order Set, allowed for an education tool and rationale to be readily available to the medical team, which was composed of physicians of various levels of experience. This availability of pre-selected rational dosing regimens of IV furosemide led to a decrease in the large variation previously seen. Further evaluation also revealed an impact of the La6 protocol on improved timeliness with no increase in adverse effect. On an institutional level, this practice change also impacted interprofessional communication and collaboration. The protocol was designed to change the pre-existing accepted relationship between the medical staff and beside RNs. Utilizing a concise monitoring tool and pre-set boundaries allowed for the restructuring of interprofessional allocation of responsibilities. Nurses were empowered to adjust furosemide dosing within 48 hours of protocol care, without delays in communication with various medical team members. In potential future uses at other institutions, other healthcare professionals, including nurse practitioners, could use this protocol. However, at the institutional level, we did not achieve sufficient uptake of the intervention to properly assess impact on hospital length of stay and we have not performed an analysis of cost efficiency, which would be an important future direction. A large proportion of patients not eligible to be placed on the La6 protocol were Lasix-naïve patients, specifically those who were not taking a home dose of oral furosemide. To benefit these patients, a Lasix-naïve protocol was also developed using a very similar design, with lower starting doses of IV
furosemide. As this protocol was in the early stages of development and implementation, evaluation was not performed. In the future, utilizing a protocol specific to patients who are Lasix naïve, in addition to a protocol geared toward Lasix-experienced patients, would increase coverage of care and potentially impact heart failure processes of care on a greater meso level scale.

The last important level of impact to be addressed is the macro level. Assessment of this intervention on a macro level would require scaling the intervention to be implemented in multiple institutions, both smaller and larger, across the region. As discussed in Section 6, this next step would involve designing a cluster-randomized trial with a sufficient sample of hospital sites to produce statistically efficient results, or to rollout to multiple institutions in a stepped wedge study design. This step would fit into the Institute for Healthcare Improvement’s Framework for Spread. This framework is designed to help institutions properly scale their pilot interventions through identification of 6 major factors that contribute to successful spread of an innovation (P. M. Barker, Reid, & Schall, 2016; K. Nolan, Schall, Erb, & Nolan, 2005). These factors include social science, organizational structure, networks and strong leadership behaviour. In addition to the process and outcome measures evaluated in this work, there are several potential additional markers that would be beneficial to assess in a multi-center analysis. As mentioned above, hospital length of stay is a clinical marker that could be used to assess global impact of such an intervention at an institution. It must, however, be said that length of stay is a very complex and crude marker for evaluating a practice change in a specific population of classically older patients, who potentially have other comorbid conditions usually complicating their hospital stay. A potentially balancing marker of hospital length of stay is the readmission rate of AHF patients treated on the protocol. This could serve as a valuable
balancing measure in future assessments. Additional balancing measures could include qualitative evaluation of medical and nursing staff satisfaction upon utilization as well as patient perceptions about the quality of care change.

The work presented in this thesis document suggests that the La6 protocol intervention to improve diuretic management in acute heart failure patients admitted to hospital warrants further study to examine feasibility and impact of the intervention on a broader, multi-site scale.
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