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International Journal of Clinical Nephrology

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Research Article

Protocolized Diuretic Strategy as a Treatment Algorithm for Cardiorenal Syndrome

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Received Date: August 26, 2022; Accepted Date: September 19, 2022; Published Date: September 29, 2022

Citation: Kelly V. Liang, Francis Pike (2022). Protocolized Diuretic Strategy as a Treatment Algorithm for Cardiorenal Syndrome. *International Journal of Clinical Nephrology*. 4(3); DOI:10.31579/2834-5142/040

Abstract

Background: A diuretic strategy is needed that is superior to current clinical care in the management of cardiorenal syndrome. Current HF guidelines do not provide any standard protocol for diuretic dosing.

Aim: To determine if a protocolized diuretic treatment strategy (ProDiuS), compared to usual care (UC), results in improved decongestion, clinical outcomes, and health-related quality of life (HRQOL), while preserving renal function in hospitalized patients with cardiorenal syndrome.

Materials and Methods: This trial was a prospective randomized single-blind trial of participants hospitalized for cardiorenal syndrome from November 1, 2013 to July 9, 2015. Participants were randomized to ProDiuS vs. UC and followed daily in hospital, and at 1-month and 3-month follow-up. ProDiuS was a stepped diuretic strategy targeting daily urine output of 3-5 L/day. UC was care at the discretion of treating providers. The primary outcome, change in body weight (kg) from randomization to 96 hours (day 4), was compared between the ProDiuS and UC groups using the t-test. Data analysis for secondary outcomes between the two groups were conducted using the t-test or Wilcoxon rank sum test depending on whether data was skewed for continuous variables, as well as linear regression modeling. For ordinal variables or proportions, data were analyzed using the exact chi-square test and logistic regression modeling. For mortality, time to death was analyzed as time-to-event data, with censoring at the time of death, date of last follow-up, or the end of the study (3 month follow-up), using Kaplan-Meier curves and log-rank tests, and Cox proportional hazards models to adjust for continuous and discrete covariates in the survival analysis.

Results: The study did not enroll the prespecified number of subjects due to slow recruitment. Out of 786 prescreened patients, 19 participants were included in the trial. There were no significant differences in baseline characteristics. Mean age was 68.7±7.3 years and 72.2% were male. There was borderline higher change in body weight from baseline to day 4 or discharge in ProDiuS vs. UC (-6.12 vs. -2.07 kg; p=0.05). Net negative fluid balance, length of hospitalization, HF rehospitalizations, mortality, acute kidney injury, adverse outcomes, and HRQOL scores were similar between groups.

Conclusion: Due to small sample size, firm conclusions cannot be drawn. However, these findings suggest that ProDiuS results in similar clinical and HRQOL outcomes as UC in HF patients treated at a large tertiary medical center in the short term. This trial was conducted in an advanced HF population on specialized HF services, which may have attenuated the efficacy of ProDiuS vs. UC. Further studies with larger sample size and more diverse HF populations are needed to determine the efficacy and safety of ProDiuS. Several lessons learned in attempting to design a trial of protocolized diuretic strategy in the cardiorenal population are discussed.

Keywords: heart failure; protocolized diuretic strategy; cardiorenal syndrome; cardiorenal failure; health-related quality of life

Introduction

Heart failure (HF) accounts for over 1 million hospital admissions annually in the United States and is a leading cause of disability and healthcare costs. It affects at least 5 million Americans and its incidence approaches 10 per 1,000 population after age 65 [1]. Cardiorenal syndrome and worsening renal function are increasingly recognized as independent risk factors for morbidity and mortality in HF [2-17]. Effective volume

removal, generally manifested by a decrease in body weight, is one of the most important goals of treatment in cardiorenal syndrome. Venous congestion may play an important role in worsening renal function due to increased renal interstitial pressure [18-21]. Therefore, effective volume removal may potentially prevent worsening renal function in addition to improving symptoms of volume overload such as edema, dyspnea, and orthopnea.

Medical therapeutic options are suboptimal in patients with advanced cardiorenal syndrome. In patients with volume overload, medical therapy focuses on sodium and fluid restriction, diuretics, blockade of the renin-angiotensin-aldosterone system, vasodilators, and inotropes [22-27]. When medical therapies fail, ultrafiltration (UF) may be used for mechanical fluid removal using dialysis or UF machines [22-30].

UF can effectively remove fluid in HF patients, but its precise role in the therapy of cardiorenal failure is still unclear. UF has been recognized as a viable treatment option by the American College of Cardiology/American Heart Association (ACC/AHA) and Heart Failure Society of America (HFSA) for diuretic resistant HF (strength of evidence = B) [24-27]. The randomized controlled trial Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated HF (UNLOAD) [28] suggested that weight and fluid loss at 48 hours was greater in the UF than the standard care (SC) group, though change in dyspnea score was not statistically significant. Rates of rehospitalization and days of hospitalization were significantly lower in the UF than the SC group. However, the multicenter randomized controlled trial (CARRESS-HF) suggested that UF is not more effective than a stepped pharmacologic diuretic regimen and raised concerns regarding the safety of UF as a treatment strategy in cardiorenal syndrome due to a higher rate of renal adverse events in the UF group [29]. Therefore, initial therapy of acute decompensated HF (ADHF) remains focused on decongestion using diuretics. A diuretic strategy is needed that is superior to current clinical care in the management of cardiorenal syndrome.

Current HF guidelines do not provide any standard protocol for diuretic dosing. The variation in usual clinical care may explain the long hospital stays and worsening renal function common in these patients. One retrospective observational study compared a diuretic dosing protocol to usual diuretic therapy for patients admitted with ADHF in a single center during a 1-year period [30]. This study found that protocol diuretic dosing was associated with larger weight loss and lower risk of 30-day readmission compared to usual diuretic dosing. Hence, we conducted a pilot randomized controlled trial in hospitalized patients with cardiorenal syndrome to determine if a protocolized diuretic treatment strategy (ProDiuS), as opposed to usual clinical care, results in improved clinical decongestion based on change in body weight at day 4 or hospital discharge (whichever comes first). Secondary aims were to compare other important clinical endpoints, such as patient symptoms, other volume measurements, hospital LOS, rehospitalization rates, mortality, renal function, laboratory markers, and HRQOL indices, between the two groups. In addition, it assessed novel and innovative biomarkers, including non-invasive Doppler ultrasound of the internal jugular vein to assess venous compliance and cystatin C for assessment of renal function.

Materials and Methods

This study was a prospective, randomized, single-blind controlled trial with allocation concealment that enrolled adult patients aged 21 years or above who were admitted for HF exacerbation to the University of Pittsburgh Medical Center (UPMC) with cardiorenal syndrome with evidence of volume overload despite standard medical therapy [24-27]. The inclusion and exclusion criteria are outlined in **Table 1.** Participants were recruited over 1.5 years.

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Age ≥21 years	Use of inotropes (at time of screening)
History of heart failure (HF), with either left ventricular (LV) dysfunction (EF<40%) or at least stage I diastolic or right ventricular (RV) dysfunction based on echocardiogram (ECHO) within the last year or diagnosis of HF by International Classification of Diseases (ICD-9)	Acute indications for hemodialysis (HD) (e.g., severe hyperkalemia, metabolic acidosis, uremic signs or symptoms, pericardial friction rub)
Evidence of renal dysfunction based on one of the following: • Estimated glomerular filtration rate (GFR) 15-59 mL/min/1.73 m^2 based on the Modification of Diet in Renal Disease (MDRD) equation using serum creatinine (Cr) obtained within 6 months of admission • Elevated Cr above upper limits of normal • An increase in serum Cr of ≥0.3 mg/dL or ≥50% from baseline on admission or during diuretic therapy, with no alternative cause for worsening renal function, while demonstrating signs and symptoms of persistent volume overload occurring within 7 days before admission or during hospitalization	Specific forms of HF by chart diagnoses: 1) Congenital heart disease 2) Primary valvular heart disease due to severe valvular stenosis or acute severe valvular regurgitation or valvular disease requiring immediate surgical repair 3) Infiltrative cardiomyopathies 4) Pulmonary hypertension (PH) as defined by World Health Organization (WHO) group I and WHO group IV
Evidence of volume overload by clinical and/or radiographic features, with at least 2 of the following: 1) peripheral edema ≥2+; 2) jugular venous distension ≥7 cm; 3) radiographic pulmonary edema or pleural effusion; 4) enlarged liver or ascites; 5) pulmonary rales, paroxysmal nocturnal dyspnea, or orthopnea; 6) elevated brain natriuretic peptide (BNP) level; 7) documentation of elevated right heart filling pressures by pulmonary artery catheter or right heart catheterization	End-stage renal disease (ESRD) requiring chronic dialysis or estimated GFR <15 mL/min/1.73 m^2 by MDRD equation (i.e., pre-existing ESRD)

	Prior use of ultrafiltration (UF) or HD in the 3 months preceding hospitalization
	Prior cardiac or kidney transplantation
	Intravascular volume depletion based on clinical assessment
	Cardiogenic shock and/or systolic blood pressure (SBP) <90 mmHg
	Unstable coronary disease or acute coronary syndrome within 1 month of admission
	Alternative explanation for worsening renal function (e.g., obstructive nephropathy, contrast-induced nephropathy, acute tubular necrosis, intrinsic renal diseases)
	Life expectancy < 3 months due to other chronic health conditions (e.g., end-stage liver disease, pulmonary disease, malignancy, etc.)
	Psychiatric disorder requiring admission to a psychiatric hospital during HF admission
	Previous enrollment in this trial or other diuretic or UF trial in the prior 3 months
	Expected geographic unavailability for 3 months following hospital admission
	Pregnancy
	Inability to provide informed consent
	Physician's assessment that use of the protocol could be unsafe or lead to adverse consequences for the patient

All participants were treated with standard HF therapies [22-27] and were maintained on a low sodium diet (≤2000 mg/day) and fluid restriction (≤1.5 L/day if serum sodium ≥130 mEq/L or ≤1 L/day if serum sodium <130 mEq/L). All participants had daily weights checked using the same standard scale each day without shoes on, before breakfast and post voiding (if possible), and accurate intake and output volumes were recorded daily per inpatient nursing protocol. Participants randomized to the *Protocolized Diuretic Strategy group* received escalating diuretics in an algorithm outlined in **Table 2**, based on the "stepped pharmacologic care arm" used by the CARRESS-HF trial investigators [29], which was proven to be equivalent if not superior to mechanical fluid removal via UF with less potential adverse effects than UF. Participants randomized to the *Usual Care group (control arm)* received escalating diuretics and medical therapy per HF guidelines published by the ACC/AHA and HFSA [24-27], dosed at the discretion of the treating cardiologist. Participants in both groups continued all other standard HF medications as recommended in HF treatment guidelines [24-27].

Participants could start isolated UF as rescue therapy, and they could also start dialysis at the discretion of the treating nephrologist.

Table 2: Protocolized Diuretic Strategy

AT RANDOMIZATION (Day 0)

UO > 5 L/day → Reduce current diuretic regimen

UO 3-5 L/day → Continue current diuretic regimen

UO < 3 L/day → See table – increase current diuretic regimen

Diuretic Dose Level	Current Dose Loop Diuretic (Furosemide IV)	Current Dose Thiazide Diuretic	Suggested Dose Loop Diuretic (Furosemide IV)*	Suggested Dose Thiazide Diuretic (Metolazone PO)
1	≤ 80 mg/day	+ or -	40 mg IV bolus + 5 mg/hr	0
2	81-160 mg/day	+ or -	80 mg IV bolus + 10 mg/hr	5 mg metolazone QD
3	161-240 mg/day	+ or -	80 mg IV bolus + 20 mg/hr	5 mg metolazone BID
4	>240 mg/day	+ or -	80 mg IV bolus + 30 mg/hr	5 mg metolazone BID

QD = once daily; BID = twice daily. IV = intravenous; PO = orally.

NOTE: Alternative loop diuretics or thiazide diuretics at equivalent doses may be used if contraindications to furosemide or metolazone exist. For example, for loop diuretics, furosemide 20 mg = torsemide 10 mg = bumetanide 1 mg; for thiazide diuretics, metolazone 5 mg PO = chlorothiazide 500 mg IV.

*Bolus doses of IV loop diuretic are to be given only at the initiation of continuous IV loop diuretic infusion. Subsequent increases or decreases in the diuretic require changing only the continuous infusion dose (not administration of a repeat IV bolus dose of loop diuretic).

AT 24 HOURS (Day 1)

Persistent Volume Overload Present

UO > 5 L/day → Reduce current diuretic regimen

UO 3-5 L/day → Continue current diuretic regimen

UO < 3 L/day → Advance to next step on table

AT 48 HOURS (Day 2)

UO > 5 L/day → Reduce current diuretic regimen

UO 3-5 L/day → Continue current diuretic regimen

UO < 3 L/day → Advance to next step on table and consider:

Dopamine or dobutamine at 2 μg/kg/hr if SBP <110 mmHg and EF<40% or RV systolic dysfunction. Nitroglycerin or Nesiritide if SBP > 120 mmHg (any EF) and severe symptoms

AT 72 HOURS (Day 3)

UO > 5 L/day → Reduce current diuretic regimen

UO 3-5 L/day → Continue current diuretic regimen

UO < 3 L/day → Advance to next step on table and consider:

Dopamine or dobutamine at 2 μg/kg/hr if SBP <110 mmHg and EF<40% or RV systolic dysfunction. Nitroglycerin or Nesiritide if SBP > 120 mmHg (any EF) and severe symptoms. Advanced cardiorenal therapy including hemodynamic guided IV therapy, left ventricular assist device (LVAD), dialysis or UF.

AT 96 HOURS (Day 4)

UO > 5 L/day → Reduce current diuretic regimen

UO 3-5 L/day → Continue current diuretic regimen

UO < 3 L/day → Advance to next step on table and consider:

Dopamine or dobutamine at 2 μg/kg/hr if SBP <110 mmHg and EF<40% or RV systolic dysfunction. Nitroglycerin or Nesiritide if SBP > 120 mmHg (any EF) and severe symptoms. Advanced cardiorenal therapy including hemodynamic guided IV therapy, left ventricular assist device (LVAD), dialysis or UF.

Table 3 shows the assessment timeline for the baseline characteristics and outcome variables

Table 3: Assessment Timeline for Variables and Potential Confounders

Variables	**Brief description**	**Time points***							
BASELINE		Base	Day 1	Day 2	Day 3	Day 4	D/C	1 mo	3 mo
Demographics	Age, Gender, Race, Ethnicity	X							
Socioeconomic status	Education, Working status, Zip code	X							
Comorbid conditions	HTN, DM, COPD, CAD, Depression (current), atrial fibrillation, hyperlipidemia, stroke, PVD, CABG, ICD, CRT	X							
Health Habits	Tobacco, Alcohol, Caffeine, Drug use	X							
Type of cardiomyopathy	Based on EF, Based on type	X							
ECHO data	LVEF, RV function, MR degree, TR degree	X							X
Volume Assessments	JVP by physical exam, edema	X	X	X	X	X	X	X	X

Anthropometrics	Weight (kg) Height (m), BMI	X X	X	X	X	X	X X	X X	X X
Vital Signs	Heart rate (HR), Blood pressure (BP)	X				X	X	X	X
Medications	• Loop diuretics • Thiazide diuretics • Other cardiac meds (Beta-blockers, ACE-I, ARB, Aldosterone antagonists, Digoxin, Nitrates) • Psychoactive medications (Antidepressants, narcotics)	X X X X	X X	X X	X X	X X	X X X X	X X X X	X X X X
HF severity class	NYHA functional class	X						X	X
Renal function	Cr Cystatin C	X X	X	X	X	X	X	X X	X X
Other laboratory data	Na, K, CO_2, Ca, Phos, BUN, Hb BNP, albumin, prealbumin Other**	X X X	X	X	X	X	X	X X	X X
PRIMARY OUTCOME									
Change in body weight at day 4 or hospital discharge	Weight (kg) from randomization to day 4 or date of discharge (whichever comes first)					X	X		
SECONDARY OUTCOMES									
1. Clinical Outcomes	Length of hospitalization						X		
	HF rehospitalizations							X	X
	Mortality & Cause of Death							X	X
2. Volume Status	Venous compliance by RIJV Doppler Ultrasound (on subset of participants)	X						X	
	Fluid balance	X	X	X	X	X	X	X	X
	Urine output	X	X	X	X	X	X		
	Clinical decongestion	X					X	X	X
3. HRQOL Outcomes									
General HRQOL	SF-36 questionnaire	X						X	X
Heart failure specific	KCCQ SAS functional class NYHA functional class	X						X	X
Depression	PHQ-9 Depression Index	X						X	X
Sleep and fatigue	PSQI ESS FACIT-F	X						X	X
4. Renal Outcomes	Change in renal function	X	X	X	X	X	X	X	X
	Need for UF or RRT	X	X	X	X	X	X	X	X
	Acute kidney injury	X	X	X	X	X	X	X	X
ADVERSE EVENTS	Hypokalemia	X	X	X	X	X	X	X	X
	Hypotension	X	X	X	X	X	X	X	X
	Hyponatremia	X	X	X	X	X	X	X	X
	Arrhythmias	X	X	X	X	X	X	X	X
	Cramps	X	X	X	X	X	X	X	X
	Other	X	X	X	X	X	X	X	X

Base = Baseline assessment at randomization in hospital. Day 1, Day 2, Day 3, and Day 4 = 1, 2, 3, and 4 days after randomization in hospital. D/C = Discharge from hospital. 1 mo and 3 mo = 1 month and 3 month follow-up visits in HF clinic.

*There was a 2-week window for 1-month follow-up and a 4-week window for 3-month follow-up visit to be considered compliant with the study visit.

**Extra tubes of blood (serum and plasma) were collected for other research bloodwork (e.g., markers of inflammation, oxidative stress, activation of the renin-angiotensin-aldosterone system, sympathetic nervous system, and endothelin). These vials were stored at -80 °C. A random urine sample was collected for storage for future studies of urinary biomarkers of acute kidney injury and cardiorenal syndrome.

The primary response variable was the change in body weight (kg) from randomization to 96 hours (day 4) or hospital discharge (whichever comes first). The secondary outcome variables included those for 1) clinical outcomes, 2) volume status, 3) HRQOL, and 4) renal outcomes. Adverse outcomes included hypokalemia, hypotension, hyponatremia, arrhythmias, cramps, and other. Participants were followed in the hospital at enrollment (day 0), day 1, 2, 3, 4, and discharge, and then at 1-month and 3-month follow-up visits.

Based on the primary response variable of change in body weight (kg), we calculated sample size estimates needed to maintain a Type I error rate (α) of 0.05 and power (1-β) of 80%. The standard deviation (σ) of the mean change in body weight was estimated to be 3.1 to 3.5 kg (6.8 to 7.7 lb). Clinically meaningful differences (δ) for the mean change in body weight were 1 to 2 kg (2.2 to 4.4 lb). We calculated the sample size would range from 38 (using the smallest σ and largest δ) to 193 (using the largest σ and smallest δ) per treatment group. The final sample size estimate was 75 per group (total N = 150), corresponding to σ = 3.2 kg and δ = 1.5 kg. We analyzed drop-ins, drop-outs, withdrawals, and non-adherences according to intention-to-treat principles.

The *primary outcome*, change in body weight (kg) from randomization to 96 hours (measured in the hospital on standard scales without shoes) was compared between the Protocolized Diuretic Strategy and Usual Care groups using the t-test. Data analysis for the *secondary outcomes* between the two groups were conducted for continuous data using the t-test if data are normally distributed or Wilcoxon rank sum test if data are skewed, as well as linear regression modeling. For ordinal variables or proportions, data were analyzed using the exact chi-square test and logistic regression modeling. For mortality, time to death was analyzed as time-to-event data, with censoring performed at the time of death, date of last follow-up, or the end of the study (3 month follow-up). Kaplan-Meier curves and log-rank tests were used to compare the groups if the proportional hazards assumption was met; otherwise, weighted log-rank tests were used. Cox proportional hazards models were used to adjust for continuous and discrete covariates in the survival analysis. Definitions of the secondary endpoints were as follows:

Clinical Status Outcomes:

1. Mean length of hospitalization – Days from admission date to discharge date.

2. Overall and HF rehospitalizations – At 1-month and 3-month follow-up visits, number of total and HF rehospitalizations.

3. Mortality – Time to death, including overall mortality (time to death from any cause) as well as cause-specific cardiovascular mortality (time to death from HF, MI, arrhythmias, or valvular disorders).

Volume Status Outcomes:

1. Venous compliance by RIJV Doppler Ultrasound [31] – Mean change in right internal jugular vein (RIJV) cross sectional area (CSA) with Valsalva. A larger change in RIJV CSA suggests greater decongestion and better venous compliance. We also compared the proportion of participants who have >17% change in RIJV CSA with Valsalva (surrogate for normal right atrial pressure (RAP) suggesting decongestion) between the two groups [31].

2. Fluid balance and urine output – Mean volume of negative fluid balance and total urine output per 24 hours were compared between the groups for each day during the intervention period (at 24 h, 48 h, 72 h, and 96 h).

3. Clinical decongestion – Defined based on jugular venous pressure of < 8 cm of water, no more than trace peripheral edema, and the absence of orthopnea. The proportion of participants in each group who met clinical decongestion was compared between the groups for each day during the intervention period (at 24 h, 48 h, 72 h, and 96 h) and at 1-month and 3-month follow-up visits.

HRQOL Outcomes:

HRQOL questionnaire scores were compared between treatment groups at both 1-month and 3-month follow-up visits [32-79]. Analyses included:

1. 36-item Short-Form Health Survey (SF-36) Physical Component Score (PCS)
2. SF-36 Mental Component Score (MCS)
3. Pittsburgh Sleep Quality Index (PSQI) global score
4. Patient Health Questionnaire-9 (PHQ-9) score (a depression severity index)
5. Heart failure-related HRQOL outcomes:
    a. Kansas City Cardiomyopathy Questionnaire (KCCQ) overall and clinical scores
    b. Minnesota Living with Heart Failure Questionnaire (MLHFQ) score
    c. Specific Activity Scale [SAS]
    d. New York Heart Association [NYHA] functional classes

Renal Outcomes:

Renal Outcomes were assessed between the groups daily during the trial protocol (at 24 h, 48 h, 72 h, and 96 h) as well as at 1-month and 3-month follow-up visits [80-87]. Analyses included:

1. Change in creatinine (Cr) and cystatin C [86]

2. Need for ultrafiltration (UF) or renal replacement therapy (RRT)

3. Acute kidney injury (AKI) – proportion of participants who had rise in Cr ≥0.3 mg/dL

The University of Pittsburgh Institutional Review Board (IRB) approved this study (approval reference number PRO13040071). All subjects provided written informed consent prior to enrollment into the study. An Internal Data and Safety Monitoring Board (IDSMB) provided oversight of subject recruitment, adverse events, serious adverse events, safety concerns, and ethical considerations throughout the study. This study is registered with ClinicalTrials.gov (Identifier: NCT01921829).

Results

Figure 1 shows the screening and randomization scheme from the time of hospital admission to the point of randomization and initiation of intervention (Protocolized Diuretic Strategy) vs. control (Usual Care). Enrollment into the ProDiuS study began on November 1, 2013. A total of 786 patients were prescreened for enrollment, and 19 participants were eventually recruited and randomized into the study. Enrollment pace was slower than anticipated, and multiple efforts were made to expand and

improve recruitment throughout the enrollment period. Despite these efforts, due to markedly lower-than-projected recruitment of study participants, at the recommendation of the Internal Data and Safety Monitoring Board (IDSMB), the study was suspended and closed earlier than anticipated in July 2015.

Figure 1: Screening and Randomization Scheme

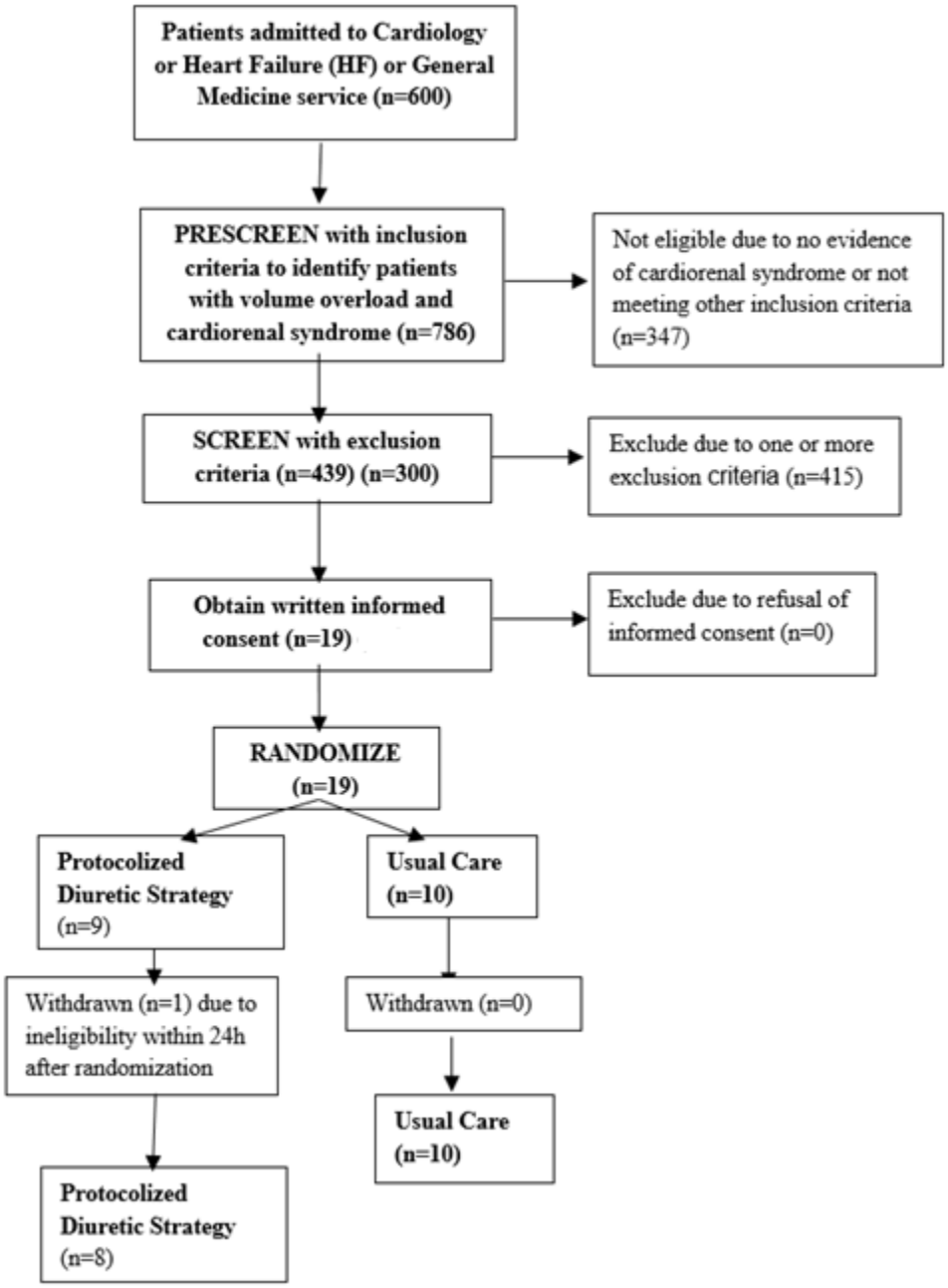

Table 4 shows the baseline characteristics of participants in the ProDiuS (n=8) and Usual Care (n=10) groups. All demographics, type and severity of HF, medication use, comorbidities, renal function, and brain natriuretic peptide (BNP) level were similar between the groups.

The mean age was 68.7±7.3 years and 72.2% were male. The majority (55.6%) had ischemic cardiomyopathy.

Table 4: Baseline Characteristics

Variables	All	ProDiuS	Usual Care	P-value*

Days in Study	92.6 ±35.6	81.7±41.9	102.4±28.4	0.23
Age	68.7±7.3	68.4±6.9	68.9±8.6	0.88
Male	13/18 (72.2)	6/8 (75.0)	7/10 (70.0)	1.00
Race				0.14
White / Caucasian	14/18 (77.8)	8/8 (100.0)	6/10 (60.0)	
Black / African American	3/18 (16.7)	0 (0.0)	3/10 (30.0)	
Asian / Indian	1/18 (5.6)	0 (0.0)	1/10 (10.0)	
Years of Education	13.2±2.3	12.9±2.4	13.5±2.3	
Smoking				0.37
Current	0 (0.0)	0 (0.0)	0 (0.0)	
Past	11/18 (61.1)	6/8 (75.0)	5/10 (50.0)	
Never	7/18 (38.9)	2/8 (25.0)	5/10 (50.0)	
Alcohol use	3/18 (16.7)	2/8 (25.0)	1/10 (10.0)	0.56
Caffeine use	14/17 (82.4)	6/8 (75.0)	8/9 (88.9)	0.58
Cardiomyopathy Type				0.15
Ischemic	10/18 (55.6)	5/8 (62.5)	5/10 (50.0)	
Dilated	3/18 (16.7)	2/8 (25.0)	1/10 (10.0)	
Hypertensive	1/18 (5.6)	1/8 (12.5)	0 (0.0)	
Other	4/18 (22.2)	0 (0.0)	4/10 (40.0)	
NYHA Class				0.60
I - Mild, no limitation	0 (0.0)	0 (0.0)	0 (0.0)	
II - Mild, slight limitation	4/15 (26.7)	2/6 (33.3)	2/9 (22.2)	
III - Moderate	9/15 (60.0)	4/6 (66.7)	5/9 (55.6)	
IV - Severe	2/15 (13.3)	0 (0.0)	2/9 (22.2)	
LVEF (%)				0.72
20-25	5/15 (33.3)	2/7 (28.6)	3/8 (37.5)	
25-30	2/30 (13.3)	2/7 (28.6)	0 (0.0)	
30-35	1/15 (6.7)	0 (0.0)	1/8 (12.5)	
RV Function				0.23
Normal	8/14 (57.1)	5/6 (83.3)	3/8 (37.5)	
Reduced (mild or moderate)	6/14 (42.8)	1/6 (16.7)	5/8 (62.5)	
MR	7/13 (53.9)	3/6 (50.0)	4/7 (54.1)	1.00
TR	10/14 (71.4)	4/6 (75.0)	6/8 (75.0)	1.00
JVP Elevated	13/17 (76.5)	7/8 (87.5)	6/9 (66.7)	1.00
Edema Grade				0.10
2	9/16 (56.3)	2/7 (28.6)	7/9 (77.8)	
3	4/16 (25.0)	3/7 (42.9)	1/9 (11.1)	
HTN	16/18 (88.9)	7/8 (87.5)	9/10 (90.0)	1.00
Diabetes	10/17 (58.8)	5/8 (62.5)	5/9 (55.6)	1.00

COPD	5/17 (19.4)	3/8 (37.5)	2/9 (22.2)	0.76
CAD	11/17 (64.7)	6/8 (75.0)	5/9 (55.6)	1.00
Depression	4/17 (23.5)	2/8 (25.0)	2/9 (22.2)	1.00
Stroke	4/17 (23.5)	0 (0.0)	4/9 (44.4)	0.07
PVD	4/18 (22.2)	0 (0.0)	4/10 (40.0)	0.04
Hyperlipidemia	10/17 (58.8)	5/8 (62.5)	5/9 (55.6)	1.00
Afib	11/18 (61.1)	6/8 (75.0)	5/10 (50.0)	1.00
CABG	6/17 (35.3)	3/8 (37.5)	3/9 (33.3)	1.00
ICD	7/18 (38.9)	2/8 (25.0)	5/10 (50.0)	0.31
CRT	2/17 (11.8)	1/8 (12.5)	1/9 (11.1)	1.00
Diuretic dose (furosemide equivalent, mg)	214.2±99.7	166.3±55.5	242.5±112.7	0.07
Cr	2.0±0.6	2.2±0.8	1.9±0.50	0.78
BUN	45.6±27.1	56.3±38.8	38.2±12.5	0.65
BNP	710.9±578.5	530.4±363.7	855.3±690.7	0.57

*P-value for t-test (for normally distributed data) or Wilcoxon rank-sum test (for skewed data) between ProDiuS vs. Usual Care groups for continuous variables or exact chi-square test for proportions.

Table 5 summarizes the primary and secondary outcomes comparing the ProDiuS and Usual Care groups. There was a borderline higher change in body weight from baseline to day 4 or discharge (whichever came 1st) in ProDiuS vs. UC group (-6.12 vs. -2.07 kg, p=0.05). There were no significant differences between groups for net negative fluid balance; length of hospitalization; number of HF rehospitalizations; mortality; acute kidney injury (AKI) defined as a rise in creatinine ≥0.3 mg/dL; adverse outcomes; or venous compliance change from baseline to 1 month or 3 months (all p>0.05).

Table 5: Primary and Secondary Outcomes

Outcomes	**ProDiuS**	**UC**	**P-value***
Primary			
Change in body weight from baseline to day 4 or discharge	-6.12 (1.95)	-2.07 (4.84)	0.05
Decongestion adjusted by change in body weight from baseline to day 4 or discharge	0.06 (0.001, 10.0)	ref	0.28
Secondary			
Length of hospitalization	8.0 (6.5)	7.5 (12.0)	0.29
# Heart Failure Rehospitalizations	3.00	1.00	na
Total Rehospitalizations	0.5 (5.5)	0.0 (1.0)	1.00
Mortality	4/9 (22.2)	1/10 (10.0)	0.58
Fluid Balance (mL/day)	-590 (1268)	-1077 (345)	0.40
Acute Kidney Injury (N (%))	4/8 (50.0)	5/10 (50.0)	1.00
Adverse Events	3.5 (7.0)	2 (6.0)	1.00
CSA-Month1-Baseline Change	0.22 (0.57)	0.11 (1.03)	0.86
CSA-Month1-Baseline Percent Change	204.8 (333.4)	168.4 (364.3)	0.91

ProDiuS = Protocolized Diuretic Strategy; UC = Usual Care; CSA = Change in surface area of internal jugular vein.

*P-value for t-test (for normally distributed data) or Wilcoxon rank-sum test (for skewed data) between ProDiuS vs. Usual Care groups for continuous variables or exact chi-square test for proportions.

Table 6a shows the overall HRQOL scores at baseline, month 1, and month 3 for all participants in the study. **Tables 6b and 6c** show the HRQOL score changes from baseline to month 1 and from baseline to month 3 comparing the ProDiuS and Usual Care groups. There were no

significant differences between groups for HRQOL scores or change in HRQOL scores from baseline to month 1 or month 3 (all p>0.05).

Table 6a: Overall HRQOL Scores

Scores	Baseline	Month1	Month3
KCCQ Clinical	18.04 (25.15)	34.22 (26.19)	35.36 (22.32)
KCCQ Overall	20.68 (18.64)	39.34 (19.78)	39.81 (19.55)
SF-36 MCS	56.38 (9.42)	57.16 (9.12)	56.70 (7.48)
SF-36 PCS	20.92 (13.34)	34.45 (16.47)	28.40 (17.83)
PHQ-9 Depression Index	6.5 (8.0)	2.0 (5.0)	2.0 (8.0)
PSQI Total	11.94 (5.50)	9.0 (11.0)	10.0 (10.0)

Table 6b: HRQOL Score Changes from Baseline to Month 1

cores	Month 1-Baseline		P-value*
	PDS	UC	
KCCQ Clinical	19.89 (9.83)	6.64 (18.01)	0.08
KCCQ Overall	16.20 (13.93)	15.65 (14.41)	1.00
SF-36 MCS	4.96 (1.80)	-1.84 (15.41)	0.52
SF-36 PCS	11.95 (11.40)	12.31 (11.72)	1.00
PHQ9 Depression Index	-7.0 (10.0)	-3.5 (6.0)	1.00
PSQI Total	-1.0 (5.0)	-2.5 (5.0)	0.52

*P-value for t-test (for normally distributed data) or Wilcoxon rank-sum test (for skewed data) between ProDiuS vs. Usual Care groups.

Table 6c: HRQOL Score Changes from Baseline to Month 3

Scores	Month 3-Baseline		P-value*
	PDS	UC	
KCCQ Clinical	24.47 (12.29)	13.84 (17.04)	0.17
KCCQ Overall	23.00 (22.10)	9.00 (17.24)	0.17
SF-36 MCS	-0.40 (0.62)	6.06 (10.83)	0.40
SF-36 PCS	12.90 (10.61)	6.25 (18.50)	1.00
PHQ-9 Depression Index	-4.0 (7.5)	-1.00 (5.00)	0.55
PSQI Total	-4.0 (8.0)	-1.00 (5.00)	1.00

*P-value for t-test (for normally distributed data) or Wilcoxon rank-sum test (for skewed data) between ProDiuS vs. Usual Care groups.

Discussion

This study was a small randomized controlled trial assessing whether a protocolized diuretic treatment strategy (ProDiuS) leads to any difference in clinically important outcomes compared to usual care (UC). ProDiuS was modelled after the very effective treatment strategy utilized in the CARRESS trial's stepped pharmacologic arm (control group), targeting a daily urine output of at least 3-5 L/day [29]. In the CARRESS trial, the control group had less adverse events and equally efficacious volume removal as the ultrafiltration group. For this reason, we conducted this trial to determine if this pharmacologic algorithm may be superior to standard care for dosing diuretics, particularly since it was a fairly aggressive algorithm utilizing loop diuretic continuous infusion and add-on metolazone early in the treatment strategy. The small number of participants in the present trial precludes any firm conclusions regarding the efficacy of ProDiuS compared to UC. This report summarizes preliminary findings of the trial, even though no conclusions of efficacy can be made based on the small sample size. Of note, the estimated required sample size would have been smaller if different definitions of clinically meaningful difference and standard deviation were used. The justification for reporting these results lie in some of the more novel outcomes studied (e.g., multiple HRQOL outcomes and venous compliance based on inferior vena cava diameter changes with Valsalva), and more importantly, to shed light on lessons learned in attempting to design a trial of protocolized diuretic strategy in the cardiorenal population. This study represents the first trial designed to compare the ProDiuS algorithm with Usual Care.

One previous retrospective observational study compared a diuretic dosing protocol to usual diuretic therapy for patients admitted with acute decompensated HF (ADHF) in a single center during a 1-year period [30]. Using a propensity scoring model, protocol use was associated with an additional 2.63-kg weight loss (P=0.003) and significantly lower risk of 30-day readmission (OR 0.46, 95% CI 0.22-0.95, P=0.037), though there was a trend towards increased hospital length of stay (LOS). There was no difference in kidney failure, inpatient mortality, or 30-day mortality.

However, due to the retrospective nature of this study, the baseline characteristics of the two groups differed in many pertinent covariates. The authors concluded that "Given the importance of 30-day readmission rates, a more rigorous randomized prospective study is imminently needed to identify the best strategy for volume removal in patients with ADHF." Our study aimed to provide further data on the efficacy, safety, and feasibility of a protocolized diuretic dosing strategy in cardiorenal syndrome in a randomized prospective trial.

The lack of difference in efficacy between ProDiuS and UC in our trial could be due to the small number of patients enrolled, or it could reflect the practice setting in which this trial was conducted. The academic tertiary medical center in which this trial was conducted involved HF specialists who generally targeted a net negative fluid balance of 1-2 L/day using a variety of diuretic dosing strategies, typically escalating intermittent intravenous loop diuretic bolus doses before starting continuous loop diuretic infusions as suggested by the ProDiuS algorithm. Therefore, the diuretic dosing strategies between Usual Care and ProDiuS were different, but both were fairly aggressive approaches, and possibly different from what may be used on usual medical floors managed by non-HF specialists.

The single blinded nature of this study in which participants were blinded may have reduced dropout in the control group and helped to avoid biased participant reporting. However, potential biases may have arisen since the treating physicians (who were unblinded) may have been inclined to treat the Usual Care group in a more aggressive fashion or use some of the same diuretic strategies as the Protocolized Diuretic Strategy group. If this occurred, the treatment effect would potentially be diluted (making the intervention effect less significant). This contamination between groups was minimized by encouraging the cardiologists and nurses to continue to use their usual medical strategies in those not randomized to the ProDiuS group (i.e., the Usual Care group). In addition, the algorithm used for the ProDiuS group was made into a separate electronic order set which required printing through a specific electronic ordering system ("Print On Demand") which was not used for ordering diuretics in the Usual Care group, making it less likely to be followed in the routine care of patients. Medication administration review of the Usual Care group suggested that the cardiologists did not treat them increasingly with the ProDiuS strategy despite having access to the algorithm.

Although this study cannot provide firm conclusions about the efficacy of the ProDiuS algorithm compared to Usual Care, it does provide a number of insights regarding treatment of cardiorenal syndrome and the feasibility of protocolizing HF treatment. Implementation of the ProDiuS algorithm as part of this clinical trial suggests that it is feasible to create a diuretic dosing algorithm to be utilized by general internists and advanced practice providers. The algorithmic nature of the ProDiuS treatment strategy provides a guide for diuretic dosing in the treatment of HF patients that would potentially be beneficial in community settings where there are less specialized HF services. In these settings, a diuretic treatment algorithm that could be utilized by non-HF specialists (e.g., advanced practice providers or general internists) may still be useful and be adopted for its convenience and ease of use. In these less specialized settings, outcomes using the ProDiuS algorithm may differ significantly from Usual Care provided by non-HF specialists.

The lack of enrollment of adequate numbers of patients in this trial also underscores some important lessons in the recruitment for such a trial of HF patients with cardiorenal syndrome. The primary reason for exclusion of patients from this trial was the use of inotropes in patients with severe cardiorenal syndrome who otherwise would have been eligible. Specific forms of HF outlined in the exclusion criteria also accounted for a significant number of exclusions, including: 1) Congenital heart disease; 2) Primary valvular heart disease due to severe valvular stenosis or acute severe valvular regurgitation or valvular disease requiring immediate surgical repair; 3) Infiltrative cardiomyopathies; 4) Pulmonary hypertension (PH) as defined by World Health Organization (WHO) group I and WHO group IV. Discussion regarding adjustment of the exclusion criteria with the HF specialists who were most engaged in this trial revealed that almost none of them felt it would be appropriate to allow patients on inotropes at the time of screening to enroll in this trial. They also felt strongly that these specific forms of HF needed to be excluded due to vastly different pathophysiology. Overall, there was a lack of enthusiasm for widespread implementation of the ProDiuS algorithm among cardiologists in our center, likely due to the fact that utilizing the predetermined diuretic algorithm would relinquish their autonomy in diuretic dosing and strategies. It was deemed too high-risk to follow an algorithm like ProDiuS in patients who were already requiring inotropes and other advanced HF therapies.

Therefore, it seems premature to protocolize HF therapy into an algorithm in the treatment of cardiorenal syndrome in tertiary care centers in which advanced HF services are available. The usual care provided by HF specialists appears to provide similar outcomes to a protocolized diuretic strategy (ProDiuS) in terms of volume removal, symptoms, and HRQOL outcomes in the short term. Further studies are needed to determine whether there is any benefit to utilizing ProDiuS or other forms of HF treatment algorithms in cardiorenal syndrome in different practice settings and over the longer term.

Conclusions

Although firm conclusions cannot be drawn, the trial's preliminary findings suggest similar clinical outcomes and HRQOL between ProDiuS and usual care in the short term. This trial is of utmost interest to cardiologists and nephrologists, who struggle to find the optimal diuretic and medical management strategy to effectively remove excess fluid yet preserve renal function. It is highly relevant to many clinicians and the community at large, as HF and cardiorenal syndrome are a leading cause of hospitalizations and healthcare costs. If a protocolized diuretic strategy can be found that optimally removes fluid in an efficient and safe manner, it could potentially be disseminated to community physicians and/or incorporated into public policy or HF treatment guidelines to improve quality of care and reduce healthcare costs in this population with high morbidity and mortality. Algorithmic treatment strategies have been successfully studied and disseminated in other disease states, e.g., sepsis and pneumonia. However, based on our study results and lack of adequate enrollment into the trial, we conclude that protocolized diuretic treatment strategies are not yet ready for prime time in cardiorenal syndrome in academic tertiary medical centers. Further studies with larger sample size and more diverse patient populations are needed to determine whether a treatment strategy based on ProDiuS leads to improved outcomes compared to usual care in other settings such as general medical services or community hospitals with less specialized HF services.

Acknowledgements

We thank John A. Kellum, MD, CRISMA (Clinical Research, Investigation, and Systems Modeling of Acute Illness) Center, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, and Paul M. Palevsky, MD, Renal Section, VA Pittsburgh Healthcare System, University of Pittsburgh, Pittsburgh, PA for their advice and guidance throughout the conduct of the study and for their suggestions on review of previous versions of this paper. We also thank Mary Fletcher, BS, Systems Programming, Western Psychiatric Institute and Clinic, University of Pittsburgh, Pittsburgh PA for her assistance and oversight in data management throughout this trial.

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DOI: 10.37579/ijcn.2022/040