Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

ROZPRAWA

NA STOPIEŃ DOKTORA NAUK MEDYCZNYCH

lek. Paweł Siwołowski

Zastosowanie nowoczesnych metod efektywnego odwadniania u chorych z ostrą dekompensacją niewydolności serca

Application of modern methods of effective dehydration in patients with acute decompensated heart failure

Promotor: prof. dr hab. n. med. Piotr Ponikowski

Wrocław 2024

Badania przedstawione w rozprawie doktorskiej pt.: „Zastosowanie nowoczesnych metod efektywnego odwadniania u chorych z ostrą dekompensacją niewydolności serca” zostały wykonane w Ośrodku Chorób Serca 4. Wojskowego Szpitala Klinicznego we Wrocławiu kierowanym przez prof. dr hab. n. med. Waldemara Banasiaka oraz w Instytucie Chorób Serca Uniwersytetu Medycznego im. Piastów Śląskich we Wrocławiu kierowanym przez prof. dr hab. n. med. Piotra Ponikowskiego.

Promotorem pracy jest prof. dr hab. n. med. Piotr Ponikowski.

PODZIĘKOWANIA

Pragnę złożyć najserdeczniejsze podziękowania wszystkim, bez których nieocenionej pomocy i wsparcia niniejsza praca nie mogłaby powstać:

Jego Magnificencji **Prof. dr hab. Piotrowi Ponikowskiemu**, Promotorowi tej pracy, za wsparcie merytoryczne, opiekę, poświęcony czas, cierpliwość, oraz niedościgniony wzór do naśladowania w łączeniu pracy lekarza i naukowca.

Panu **Prof. dr hab. Waldemarowi Banasiakowi** za życzliwość, wyrozumiałość oraz za stworzenie ośrodka wspierającego rozwój naukowy i zawodowy lekarzy, w którym dane mi było zdobywać kolejne etapy doświadczenia zawodowego.

Przełożonym oraz Koleżankom i Kolegom z Instytutu Chorób Serca Uniwersyteckiego Szpitala Klinicznego we Wrocławiu, Kliniki Kardiologii Ośrodka Chorób Serca 4. Wojskowego Szpitala Klinicznego we Wrocławiu za owocną współpracę oraz przyjazną i motywującą atmosferę w miejscu pracy i nauki.

Szczególnie dziękuję mojej **Żonie** za ogromne wsparcie, wyrozumiałość i motywację do dalszego rozwoju.

Niniejszą pracę pragnę dedykować moim **Rodzicom**,

Anieli i Franciszkowi Siwołowskim.

SPIS TREŚCI

WYKAZ PUBLIKACJI STANOWIĄCYCH ROZPRAWĘ DOKTORSKĄ

WYKAZ PUBLIKACJI STANOWIĄCYCH ROZPRAWĘ DOKTORSKĄ

Paweł Siwołowski

Cykl

1. Jan Biegus, Robert Zymliński, **Paweł Siwołowski**, Jeffrey Testani**,** Joanna Szachniewicz, Agnieszka Tycińska, Waldemar Banasiak, Andrew Halpert, Howard Levin, Piotr Ponikowski
   Controlled decongestion by Reprieve therapy in acute heart failure: results of the TARGET-1 and TARGET-2 studies.
   Eur J Heart Fail. 2019 Sep;21(9):1079-1087. doi: 10.1002/ejhf.1533. Epub 2019 Aug 29.

2. **Paweł Siwołowski**, Piotr Gajewski, Mateusz Sokolski, Robert Zymliński, Mateusz Guzik, Joanna Szachniewicz, Piotr Ponikowski
   Diuretic treatment using the RenalGuard® system in patients hospitalized due to acute decompensated heart failure and characterization of the profile of patients with good and poor response to treatment – preliminary study.
   Cardiology Journal 2024 (*Ahead of print*) doi: 10.5603/cj.102386
   IF$_{2023}$ **2,5**

WYKAZ STOSOWANYCH SKRÓTÓW

ADHF- *ang. acute decompensated heart failure*; ostra dekompensacja niewydolności serca.

NT-proBNP- *ang. N-terminal pro-B type natriuretic peptide*; N-końcowy propeptyd natriuretyczny typu B.

WPROWADZENIE

Dane z raportu Asocjacji Niewydolności Serca Polskiego Towarzystwa Kardiologicznego wskazują, że liczba chorych z niewydolnością serca w Polsce w 2018 roku sięgała 1,25 mln[1]. Zaostrzenie objawów niewydolności serca pozostaje wciąż jedną z głównych przyczyn hospitalizacji w oddziałach szpitalnych w grupie pacjentów powyżej 65 roku życia i nadal wiąże się z dużą śmiertelnością oraz częstością ponownych hospitalizacji[2,3]. Śmiertelność wewnątrzszpitalna wśród chorych hospitalizowanych z powodu ostrej niewydolności serca (ONS) wynosi od 4 do 10%, a częstość zgonów i ponownej hospitalizacji przekracza 45% w obserwacji rocznej. W Polsce zaledwie 57% pacjentów przeżywa 5 lat od momentu rozpoznania niewydolności serca, natomiast w grupie wiekowej powyżej 75 roku życia połowa pacjentów przeżywa jedynie ok. 4 lata[4]. Najczęstszą formą manifestacji klinicznej pacjentów hospitalizowanych z powodu niewydolności serca (50-70% przypadków) jest tzw. ostra dekompensacja przewlekłej niewydolności serca (z ang. *Acute Decompensated Heart Failure* - ADHF). Wstępna ocena kliniczna chorych z dekompensacją niewydolności serca pozwala w prosty sposób zidentyfikować wśród nich cztery różne profile hemodynamiczne, w tym najliczniejszą grupę pacjentów z objawami przewodnienia, bez obniżonej perfuzji obwodowej, czyli tzw. profil „mokry-ciepły"[5].

Jednym z podstawowych celów w leczeniu chorych z ostrą dekompensacją niewydolności serca i objawami przeciążenia płynowego jest szybka i bezpieczna eliminacja przewodnienia przy zastosowaniu między innymi diuretyków pętlowych. Przewlekła aktywacja neurohormonalna (głównie układu renina-angiotensyna-aldosteron), w grupie pacjentów leczonych z powodu przewlekłej niewydolności serca, powoduje stopniowe zmniejszenie skuteczności standardowego postępowania farmakologicznego, prowadząc w konsekwencji do częściowej bądź całkowitej oporności na leczenie diuretykami i postępującego przewodnienia[6].

Opcją pierwszego wyboru w leczeniu zaostrzenia objawów przewlekłej niewydolności serca u chorych z objawami zastoju i przewodnienia pozostają diuretyki pętlowe, często w połączeniu z lekami wazodilatacyjnymi[7-10]. W trakcie standardowej terapii diuretykiem pętlowym początkowo dochodzi do usunięcia nadmiaru płynu z przestrzeni wewnątrznaczyniowej a następnie przemieszczeniu ulega objętość płynu z przestrzeni pozanaczyniowej do naczyń łożyska naczyniowego w tempie określanym jako PRR - *plasma refill rate*. Kluczowym zatem elementem bezpieczeństwa i skuteczności terapii diuretycznej pozostaje możliwość uzyskania stabilnego tempa przemieszczenia nadmiaru płynu z

przestrzeni pozanaczyniowej do łożyska naczyniowego. Jeśli tempo usuwania nadmiaru płynu z przestrzeni wewnątrznaczyniowej jest zbyt szybkie w stosunku do *plasma refill rate,* może dojść do nadmiernego opróżnienia przestrzeni wewnątrznaczyniowej, w efekcie do spadku rzutu serca i obniżenia perfuzji nerkowej, co prowadzi do aktywacji szeregu nerkowych i pozanerkowych mechanizmów retencji sodu i wody w organizmie a w konsekwencji do dalszego rozwoju oporności na diuretyki[11].

Istotnym problemem klinicznym pozostaje również współistniejąca z niewydolnością serca przewlekła choroba nerek jak i pogorszenie funkcji nerek w trakcie hospitalizacji z powodu zaostrzenia objawów niewydolności serca, które występują bardzo często i są niezależnym czynnikiem złego rokowania pacjentów z ostrą niewydolnością serca[12,13]. Istnieje zatem uzasadniona potrzeba opracowywania nowych, bezpiecznych i skutecznych metod eliminacji przewodnienia oraz monitorowania terapii diuretykami u pacjentów z ostrą niewydolnością serca.

CELE PROJEKTU BADAWCZEGO

Celem projektu była ocena zastosowania diuretyku pętlowego (furosemidu) w połączeniu z metodą kontrolowanego odwadniana z zastosowaniem systemu RenalGuard®, u pacjentów z zaawansowaną niewydolnością serca i współistniejącą przewlekłą chorobą nerek, hospitalizowanych z powodu ostrej dekompensacji niewydolności serca oraz próba identyfikacji grupy pacjentów którzy odniosą istotnie większą korzyść z tej formy terapii, na podstawie analizy potencjalnego związku pomiędzy odpowiedzią diuretyczną a profilem klinicznym tych pacjentów i stężeniami wybranych markerów biochemicznych.

MATERIAŁ I METODY

Do badania włączono pacjentów, którzy byli hospitalizowani w Klinice Kardiologii Ośrodka Chorób Serca 4. Wojskowego Szpitala Klinicznego we Wrocławiu z powodu wystąpienia ADHF (ostrej dekompensacji niewydolności serca). ADHF była diagnozowana na podstawie obowiązujących wówczas wytycznych Europejskiego Towarzystwa Kardiologicznego. Przewlekłą chorobę nerek definiowano jako wartość eGFR przy przyjęciu w przedziale 25 – 90 ml/min/1,73m2 wyliczoną z równania MDRD.

W ramach rozprawy przeprowadzono dwa badania, których wyniki opublikowano w recenzowanych czasopismach międzynarodowych w formie dwóch manuskryptów:

1. Pierwsza praca jest przeprowadzoną w sposób nierandomizowany, prospektywną analizą terapii 19 pacjentów z przewlekłą chorobą nerek, hospitalizowanych z powodu ostrej dekompensacji niewydolności serca (klasa NYHA III-IV, RR 125 ± 14 / 73 ± 16 mmHg, eGFR 58 ± 24) z utrzymującymi się objawami przewodnienia, w której oceniano czy zastosowanie systemu RenalGuard® w połączeniu ze standardową terapią opartą na diuretyku pętlowym dożylnie poprawi efektywność odwadniania chorych z ADHF.
2. Druga praca jest retrospektywną, ukierunkowaną analizą porównawczą wybranych parametrów klinicznych i biochemicznych w celu szczegółowego określenia parametrów związanych z lepszą odpowiedzią diuretyczną i największą korzyścią kliniczną po zastosowanej terapii z zastosowaniem systemu RenalGuard®.

Badania przeprowadzono za zgodą lokalnej Komisji Bioetycznej Dolnośląskiej Izby Lekarskiej i Komisji Bioetycznej przy Uniwersytecie Medycznym we Wrocławiu (opinia nr KB – 210/2019) oraz zgodnie z zasadami dobrej praktyki klinicznej (Good Clinical Practice) i Deklaracji Helsińskiej. Wszyscy pacjenci, przed włączeniem do badania, wyrazili świadomie pisemną zgodę na udział w badaniu.

Najważniejsze kryteria włączenia do badania obejmowały:

1. pierwotne rozpoznanie ostrej niewydolności serca jako przyczyny hospitalizacji
2. kliniczne objawy przewodnienia (pomimo standardowego leczenia ostrej niewydolności serca z zastosowaniem furosemidu dożylnie), które obejmowały: utrzymującą

się duszność spoczynkową lub przy minimalnym wysiłku fizycznym w trakcie badania przesiewowego i w czasie rekrutacji, trzeszczenia u podstawy płuc, obrzęki obwodowe ≥ +1 (w skali 0-3 +) w badaniu fizykalnym oraz radiologiczne objawy zastoju w krążeniu płucnym w zdjęciu przeglądowym rtg klatki piersiowej.

3. podwyższone stężenie peptydów natriuretycznych: BNP (peptyd natriuretyczny typu B) ≥ 500 pg / ml lub NT-proBNP (peptyd natriuretyczny typu N-terminalny pro-B) ≥ 2000 pg / ml; u pacjentów w wieku ≥ 75 lat lub z aktualnym migotaniem przedsionków (w momencie włączenia), BNP ≥ 750 pg / ml lub NT-proBNP ≥ 3000 pg / ml.

4. skurczowe ciśnienie tętnicze ≥100 mmHg na początku i na końcu badania przesiewowego

5. wcześniej występującą przewlekłą chorobę nerek zdefiniowaną jako wartość szacunkowego współczynnika przesączania kłębuszkowego (eGFR) pomiędzy prezentacją i włączeniem do badania ≥ 25 i <90 ml / min / 1,73 m2, obliczoną przy użyciu równania MDRD.

Pacjentów leczonych furosemidem podawanym dożylnie w ciągu pierwszych 24 godzin hospitalizacji, poddawano w czasie kolejnych 24 godzin terapii łączącej furosemid podawany dożylnie z zastosowaniem systemu RenalGuard® i ustaloną przez lekarza prowadzącego terapię, objętością utraty płynów (FLL – *Fluid Loss Limit*). Cewnik infuzyjny systemu RenalGuard® łączono z pacjentem poprzez obwodowy dostęp żylny a umieszczony na wadze urządzenia zbiornik na mocz łączono w celu ciągłego monitorowania diurezy ze standardowym cewnikiem Foley'a umieszczonym w pęcherzu moczowym pacjenta. Na początku terapii wszyscy pacjenci otrzymywali 40mg furosemidu w formie bolusa dożylnego. W pierwszej godzinie terapii kontynuowano nawodnienie w stosunku 1:1 do uzyskanego efektu diuretycznego (faza *Matched Fluid Balace*), po czym ustawiano zadany bilans płynów (faza *Desired Fluid Balance*) na -100ml/h. Kolejne dawki furosemidu i schemat podawania leku (bolus dożylnie lub wlew ciągły dożylnie) ustalano na podstawie oceny stanu klinicznego pacjenta, w celu uzyskania założonego ujemnego bilansu płynowego. U wszystkich chorych oceniano objawy niewydolności serca, efekt diuretyczny, stężenia wybranych parametrów biochemicznych i biomerkerów takich jak: kreatynina, eGFR, cystatyna C, NGAL, ET-1, KIM-1 w określonych przedziałach czasowych podczas terapii, przy wypisie oraz w 30-dniowej obserwacji, a także zależności pomiędzy odpowiedzią diuretyczną a stężeniami jonów sodowych i kreatyniny w moczu. Ponadto analizowano częstość zdarzeń niepożądanych takich jak: zgon, niewydolność nerek wymagająca dializoterapii, zawał serca, udar mózgu i

przemijające ataki niedokrwienne (TIA), zaostrzenie objawów niewydolności serca, konieczność przedłużonej hospitalizacji w związku z procedurą.

Analiza statystyczna.

Zmienne ciągłe o rozkładzie normalnym opisano za pomocą średnich ± odchylenie standardowe, zmienne o rozkładzie innym niż normalny zostały opisane przez mediany z [górnymi i dolnymi kwartylami], zmienne skategoryzowane podano jako liczby i procenty. Normalność rozkładu badano z użyciem testu Shapiro-Wilka. Istotność statystyczną różnic między punktami czasowymi oceniono za pomocą testu t dla prób powiązanych lub testu Wilcoxona. Różnice pomiędzy grupami o dobrej i złej odpowiedzi diuretycznej oceniano z użyciem testu t dla prób niepowiązanych lub testu Manna-Whitney'a. $P < 0,05$ uznano za statystycznie istotne. Analizy statystyczne przeprowadzono za pomocą oprogramowania STATISTICA 13 (StatSoft Poland, Kraków, Poland).

PUBLIKACJE

1. **Controlled decongestion by Reprieve therapy in acute heart failure: results of the TARGET-1 and TARGET-2 studies.**
   Jan Biegus, Robert Zymliński, **Paweł Siwołowski**, Jeffrey Testani**,** Joanna Szachniewicz, Agnieszka Tycińska, Waldemar Banasiak, Andrew Halpert, Howard Levin, Piotr Ponikowski; Eur J Heart Fail. 2019 Sep;21(9):1079-1087.

ESC European Society of Cardiology

European Journal of Heart Failure (2019) 21, 1079–1087
doi:10.1002/ejhf.1533

RESEARCH ARTICLE

Controlled decongestion by Reprieve therapy in acute heart failure: results of the TARGET-1 and TARGET-2 studies

Jan Biegus[1,2*†], Robert Zymlinski[1,2†], Pawel Siwolowski[1,2], Jeffrey Testani[3], Joanna Szachniewicz[2], Agnieszka Tycińska[4], Waldemar Banasiak[2], Andrew Halpert[5], Howard Levin[5], and Piotr Ponikowski[1,2*]

[1]Department of Heart Diseases, Medical University, Wroclaw, Poland; [2]Centre for Heart Diseases, Military Hospital, Wroclaw, Poland; [3]Department of Medicine, Yale University, New Haven, CT, USA; [4]Department of Cardiology, Medical University of Bialystok, Bialystok, Poland; and [5]Reprieve Cardiovascular, Milford, MA, USA

Received 2 May 2019; revised 15 May 2019; accepted 17 May 2019

Aims Safe and effective decongestion is the main goal of therapy in acute heart failure (AHF). In the non-randomized, prospective TARGET-1 and TARGET-2 studies (NCT03897842), we investigated whether adding the Reprieve System® (which continuously monitors urine output and delivers a matched volume of hydration fluid sufficient to maintain the set fluid balance rate) to standard diuretic-based regimen improves decongestion in AHF.

Methods and results The population consisted of 19 patients hospitalized with AHF (mean age 67 ± 10 years, 18 male, ejection fraction 34 ± 15%, median N-terminal pro-B-type natriuretic peptide 4492 pg/mL). Patients served as their own controls: each patient underwent 24 h of standard diuretic therapy followed by 24 h of diuretics with Reprieve therapy (with normal saline used for matched volume replacement). The primary efficacy endpoint of actual fluid loss not exceeding the target fluid loss at the end of therapy was met in all 19 (100%) patients. The mean diuresis during Reprieve therapy was 6284 ± 2679 mL (vs. 1966 ± 1057 mL 24 h before therapy) and 2053 ± 888 mL (24 h after therapy) (both $P < 0.0001$). At the end of therapy, patient global assessment improved from 7.7 ± 1.1 to 3.0 ± 1.3 points ($P < 0.001$), central venous pressure decreased from 15.5 ± 5.3 mmHg to 12.8 ± 4.8 mmHg ($P < 0.05$) and the median urine sodium loss was 9.7 [3–13] mmol/h. The Reprieve therapy was safe, systolic blood pressure remained stable, mean creatinine dropped from 1.45 ± 0.4 mg/dL to 1.26 ± 0.4 mg/dL ($P < 0.001$) and biomarkers of renal injury did not change during treatment.

Conclusions The Reprieve System in conjunction with diuretic therapy supports safe and controlled decongestion in AHF.

Keywords Diuresis • Decongestion • Acute heart failure • Clinical trial

Introduction

Congestion due to volume overload or volume redistribution characterizes the majority of patients with acute heart failure (AHF). The former is mainly driven by sodium and water retention, therefore loop diuretics remain the cornerstone of therapy with fast, effective, sustained and safe decongestion as main goals of decongestion in AHF.[1–3] Notwithstanding this, there is no established evidence-based regimen for optimal diuretic use in the setting of AHF.[3–5] The objective tools to assess fluid volume, which can be safely removed from a patient within a certain time period, are still lacking, as probably being patient-dependent. Diuretic effectiveness is typically assessed upon several measures comprising change in weight, urine volume, clinical signs and symptoms of congestion relief, which are not predictive for prognosis.[6,7] Unfortunately, uncontrolled, too aggressive dehydration may lead to

*Corresponding authors. Department of Heart Diseases, Medical University, Wroclaw, University Centre for Heart Diseases, University Hospital, Borowska 213, 50-556 Wroclaw, Poland. Tel/Fax: +48 71 7331112, Email: piotr.ponikowski@umed.wroc.pl; janbiegus@gmail.com
†These authors contributed equally.

rapid deterioration of haemodynamics, neurohormonal activation and renal injury.[4,8,9] The fear of deleterious overdiuresis underlies physicians' concern to use the amount of diuretics a patient with AHF likely needs, which in practice may lead to diuretic underdosing with lack of clinical effects associated with prolonged congestion with detrimental consequences.[10]

The Reprieve-guided diuretic therapy has been designed to provide the clinician with greater control of fluid loss during diuretic administration. In the face of high urine output induced by a diuretic, the Reprieve System™ (Reprieve Cardiovascular, Milford, MA, USA) is designed to maintain intravascular fluid volume, and with it cardiac output and renal perfusion by preventing the patient's fluid loss from exceeding a clinician determined fluid loss rate. Specifically, limiting the net fluid loss rate is expected to prevent rapid deterioration of haemodynamics associated with excessive diuresis. Further, supplementing excess fluid loss with normal saline should prevent activation of compensatory mechanisms that drive the kidney to attempt to retain sodium, and with it, fluid. Combined, all of these effects have the potential to protect the kidney from renal injury that is often associated with diuretic therapy. In order to achieve this fluid balance target, the Reprieve System measures the patient's urine output constantly during therapy and infuses a volume of hydration fluid sufficient to maintain the set fluid balance rate. The same platform technology has been in use in the cardiac catheterization laboratory, where the combination of matched fluid and diuretic infusion has been found to induce much higher urine output rates than is possible with either on their own.[11] It has been demonstrated that it is able to protect patients from contrast-induced acute kidney injury.[12]

The hypothesis of the TARGET-1 and TARGET-2 trials was that this platform technology could be safely applied to hospitalized patients with AHF. The study was designed as a safety pilot study, but also included measurements to support future evaluation of the efficacy of the therapy.

Materials and methods

We present the results of the TARGET-1 and TARGET-2 trials (NCT03897842), two non-randomized, single-centre, prospective studies that ran consecutively in our institution between 2017 and 2019. This was the first-in-man use of the Reprieve System™ for controlled decongestion in AHF. Study protocols were independently approved by the local ethics committee and the studies were conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent prior to enrolment.

The Reprieve System

The Reprieve System™ comprises an automated fluid management system that measures patient's urine output and delivers volume sterile replacement solution in order to achieve a clinician set fluid balance. For example, if the desired fluid balance was programmed to −150 mL/h and the patient's urine output was 350 mL/h, the system would infuse 200 mL of sterile replacement solution to achieve the target fluid balance. The device is connected to the patient through a peripheral vein cannula and urinary catheter (*Figure 1*).

Study design and patients

The TARGET-1 and TARGET-2 studies were designed to investigate the safety and decongestive efficacy of the Reprieve System™ added to standard diuretic-based regimen in patients with AHF. Patients served as their own controls: each patient underwent 24 h of standard diuretic therapy followed by at least 24 h of diuretics with Reprieve therapy with normal saline (NaCl 0.9% Baxter) used for volume replacement.

In both studies the infusion connector of the Reprieve System™ was inserted into the patient's intravenous catheter and the urine tubing connector into the Foley catheter. Subsequently, in TARGET-1, each patient received a bolus of 40 mg furosemide intravenously followed by 1 h of matched replacement (desired fluid balance set to 0 mL/h), after which desired fluid balance was set to −100 mL/h. Although there was no pre-specified protocol of furosemide administration, a treating physician was instructed to adjust the diuretic regimen in order to maintain this negative fluid balance. During the entire period of therapy, patients were closely monitored for adverse events, particularly signs and symptoms of fluid overload and decision regarding changes in desired fluid balance, and diuretic dosing was left to the discretion of the treating physician. The TARGET-2 study followed the TARGET-1 protocol with the following changes: all patients who completed the 24 h period of standard therapy, before initiation of Reprieve therapy, received a 40 mg furosemide bolus and only those with a diuresis > 200 mL within the subsequent 4 h were eligible to continue the study (diuretic challenge). Immediately after receiving 200 mL of urine, Reprieve therapy was started with a desired fluid balance set to −200 mL/h. Similarly to TARGET-1, there was no pre-specified protocol of furosemide administration and a treating physician was instructed to adjust the diuretic regimen in order to maintain a negative fluid balance of −200 mL/h.

In both TARGET-1 and TARGET-2, there was no standard protocol of diuretic administration; however, in most cases, patients were receiving an infusion of furosemide (typically at a dose of 10 mg/h) and the diuretic dose was adjusted by a supervising physician to achieve a desired net negative fluid balance. Additionally, all patients in TARGET-2 had a central venous catheter inserted for haemodynamic monitoring.

In brief, the most important entry criteria for both studies included the following:

(i) Primary diagnosis of AHF as a reason for hospitalization.
(ii) Clinical signs of congestion (despite standard background therapy for AHF with intravenous furosemide), including persistent dyspnoea at rest or with minimal exertion at screening and at the time of enrolment, pulmonary rales, peripheral oedema ≥ +1 (on a 0–3+ scale), and pulmonary congestion on chest radiograph (all needed to be present).
(iii) Elevated natriuretic peptides: B-type natriuretic peptide (BNP) ≥ 500 pg/mL or N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥ 2000 pg/mL; for patients aged ≥ 75 years or with atrial fibrillation at the time of enrolment, BNP ≥ 750 pg/mL or NT-proBNP ≥ 3000 pg/mL.
(iv) Systolic blood pressure ≥ 100 mmHg at the start and at the end of screening.
(v) Pre-existing chronic renal failure (impaired renal function) defined as an estimated glomerular filtration rate (eGFR)

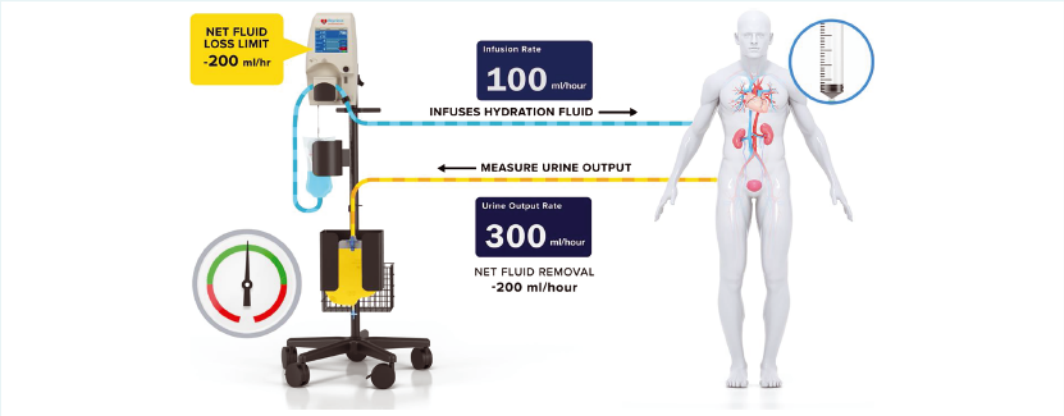

Figure 1 Scheme of the Reprieve-based therapy.

between presentation and enrolment of ≥ 25 mL/min/1.73 m^2 and < 90 mL/min/1.73 m^2, calculated using the Modification of Diet in Renal Disease (MDRD) equation.[13]

As the Reprieve System™ requires the use of a standard Foley catheter, known inability (or unwillingness) to have a Foley catheter placed was the exclusion criterion. Detailed information of all inclusion and exclusion criteria for both TARGET-1 and TARGET-2 studies as well as a flowchart of the studies are provided in the online supplementary *Appendix S1* and *Figure S1*. Baseline assessments were performed before connection of the patient to the Reprieve System™.

At baseline, and during the entire period of the Reprieve System™ procedure, close clinical evaluation was performed with regular blood and urine samples taken and haemodynamic monitoring (TARGET-2). All patients were subsequently followed up to 90 days. The study was sponsored by Reprieve Cardiovascular. The sponsor funded data collection and data monitoring. Data were reviewed by the authors and the manuscript was reviewed and approved by the authors at all stages of development.

Outcomes

The study was aimed to evaluate the safety and tolerability of the Reprieve System-based diuretic therapy in patients with AHF, with a pre-specified primary endpoint assessing the amount of fluid loss that exceeds the target fluid loss at conclusion of Reprieve therapy. As this was a first-in-man study of this therapy, this endpoint was designed to measure the Reprieve System ability to safely manage the patient's fluid balance in the setting of acutely decompensated heart failure. Serious adverse effects were reported up to 30 days.

The investigational efficacy endpoints included diuresis (measured during the study and 24 h after completion of Reprieve therapy) and the net negative balance (defined as the difference between urine output and fluid intake during treatment); both were measured/calculated hourly.

Clinical evaluation was performed at baseline and at the end of Reprieve therapy using self-reported patient global assessment (PGA) with a simple number indicating judgement of symptom severity (with 10 being the worst and 0 indicating no symptoms).

Clinical signs of congestion were also assessed by a physician, including assessments of the following:

(i) Jugular venous pressure (on a 3-point scale) describing the point of pulsation of the external jugular vein [1 (< 6 cm), 2 (6–10 cm), 3 (> 10 cm)]. For jugular venous pressure assessment, the patient was positioned at a 45° incline.
(ii) Oedema (0–3 scale) assessed on the basis of oedema area and indicating indentation of skin with mild digital pressure: 0–complete absence of skin indentation, 1–small area of oedema (ankles), indentation that resolves over 10–15 s, 2–(above ankles) indentation that resolves over 15–30 s, 3–large area of oedema that resolves slowly after > 30 s.
(iii) Pulmonary congestion (0–3 scale) assessed by lung auscultation. The scale includes: 0–no rales, 1–rales over less than one-third of the lung fields, 2–rales over one-third to two-thirds of the lung fields, 3–rales over more than two-thirds of the lung fields.
(iv) Patient's weight (kg).

Laboratory measurements in peripheral blood and urine

The following laboratory parameters were assessed using standard methods in local laboratory:

(i) Haematology: haemoglobin, haematocrit, leukocytes (white blood cell count), platelets (at baseline, at end of the procedure, and at days 30 and 90).
(ii) Blood gas/acid base balance (at baseline, every 3 h during the procedure and at discharge; additionally, in TARGET-2, samples from the right atrium were also assessed every 3 h during the procedure).
(iii) Serum electrolytes: sodium, potassium (at baseline, 12 h, end of treatment, and discharge).
(iv) Standard renal tests: creatinine, eGFR by MDRD method, blood urea nitrogen (at baseline, 12 h, end of treatment, and discharge).

(v) Plasma NT-proBNP (immunoenzymatic method, Siemens, Marburg, Germany), troponin I (immunoenzymatic method, Single Dimension RxL Max, Siemens) (at baseline, end of procedure, and discharge).
(vi) Urine spot samples: electrolytes (sodium, potassium), creatinine, urea (at baseline, 12 h, end of treatment, and discharge; additionally, in TARGET-2 hourly during the first 6 h of Reprieve therapy).
(vii) Biomarkers of kidney function/injury: serum kidney injury molecule-1 (KIM-1), urine neutrophil gelatinase-associated lipocalin (NGAL), plasma cystatin C (at baseline, 12 h, end of the procedure, and discharge).

In TARGET-2, urine volume was monitored hourly, whereas urine sodium (UNa^+) excretion (mmol/L) and net negative sodium balance (mmol) (calculated as the difference between total sodium infused and excreted) were monitored during the first 6 h of Reprieve therapy. After that, spot UNa^+ concentration was measured at 12, 18 and 24 h after Reprieve therapy to estimate sodium excretion/net sodium balance at 6 h intervals.

Haemodynamic monitoring

All patients in TARGET-2 had a central venous catheter inserted into the carotid vein. Central venous pressure (CVP) and central venous oxygen saturation were measured at baseline, at 12 h, and at the end of Reprieve therapy.

Statistical analysis

Continuous variables with a normal distribution were described using means ± standard deviation, variables with skewed distribution were described by medians with [upper and lower quartiles], categorized variables were given as numbers and percentages. The statistical significance of differences between the timepoints was assessed using paired sample *t*-test. A *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using the STATISTICA 13 (StatSoft Poland, Krakow, Poland).

Results

Baseline characteristics

The baseline characteristics of the study population [TARGET-1 ($n = 10$) and TARGET-2 ($n = 9$)] are described in *Table 1*. All screened patients entered the studies. In brief, almost all patients were male ($n = 18$), with mean age of 67 ± 10 years, mean left ventricular ejection fraction of 34 ± 15%. They had markedly elevated NT-proBNP with median [interquartile (IQR) range] of 4492 [2662–6806] pg/mL and impaired renal function with mean baseline serum creatinine and eGFR of 1.45 ± 0.4 mg/dL, 58 ± 24 mL/min/1.73 m^2, respectively. The mean length of hospital stay before initiation of Reprieve therapy was 2 ± 1 days.

Safety endpoints

The mean duration of Reprieve therapy was 25 ± 1 h. The procedure was well tolerated and none of the patients had any signs of infection nor any other procedure-related complication during and after the treatment phase. During the entire treatment period, systolic blood pressure remained stable (123 ± 24 mmHg at baseline, 115 ± 24 mmHg at 6 h, 119 ± 19 mmHg at 12 h, and 116 ± 20 mmHg at the end of Reprieve therapy; $P = 0.19$). There were neither deaths nor any serious adverse events reported in the study population until day 30.

Diuresis, net negative fluid balance and furosemide dose

The primary efficacy endpoint of preventing excess fluid loss – i.e. actual fluid loss not exceeding the target fluid loss at conclusion of Reprieve therapy – was met in all 19 (100%) patients.

Table 2 reports mean hourly diuresis, volume of 0.9% NaCl infused, and net negative fluid balance at 6 h intervals in both studies.

The pattern of diuresis in TARGET-1 showed gradual and substantial decrease from a mean of 351 ± 285 mL/h in the first 6 h to 88 ± 80 mL/h between 12 and 18 h of therapy with subsequent rise to 139 ± 160 mL/h during the final period of therapy. Negative fluid balance was stable in the first 12 h of therapy (in the mean range of 100 mL/h), and subsequently decreased during the remaining second half of therapy. In none of the 10 patients in TARGET-1 the actual fluid loss at the end of therapy exceeded the target fluid loss.

In contrast, the pattern of diuresis in TARGET-2 showed only a small decrease after the first 6 h of treatment (from a mean of 334 ± 204 mL/h to 270 ± 125 mL/h between 6 and 12 h of therapy) and remained stable until the end of therapy. All patients exceeded the new TARGET two criteria of 200 mL of urine output during the first 4 h. Negative fluid balance was stable throughout the entire treatment period and remained in the mean range of 120–130 mL/h. Again, in none of the nine patients in TARGET-2 the actual fluid loss at the end of therapy exceeded the target fluid loss.

The combined date of all therapies revealed that the mean total diuresis during Reprieve therapy were 6284 ± 2679 mL (vs. 1966 ± 1057 mL 24 h before therapy) and 2053 ± 888 mL (24 h after therapy) (both $P < 0.0001$).

Data from TARGET-1 and TARGET-2 showed that diuresis achieved during Reprieve therapy was significantly bigger compared to 24 h periods of standard diuretic therapy before and after Reprieve therapy [4859 ± 2219 mL (vs. 1865 ± 1143 mL 24 h before therapy) and 1620 ± 610 mL (24 h after therapy) for TARGET-1; and 7867 ± 2292 mL (vs. 2078 ± 1008 mL 24 h before therapy) and 2533 ± 927 mL (24 h after therapy) for TARGET-2; all $P < 0.01$]. This was related to significantly higher doses of furosemide used during Reprieve therapy in TARGET-2 compared to 24 h periods of standard diuretic therapy before and after Reprieve therapy [262 ± 98 mg (vs. 76 ± 40 mg before therapy) and 80 ± 99 mg (after therapy) in TARGET-2; both $P < 0.0001$] (online supplementary *Table 1S*). Doses of furosemide used during treatment in TARGET-1 were not higher than before and after Reprieve therapy [120 ± 43 mg (vs. 80 ± 25 mg before therapy) and 90 ± 27 mg (after therapy); both $P > 0.05$].

Table 1 Baseline characteristics of the study population

Variable	Total	TARGET-1	TARGET-2
Patients, *n*	19	10	9
Age (years)	67 ± 10	64 ± 13	70 ± 6
Male sex	18 (95)	9 (90)	9 (100)
NYHA class I/II/III/IV before inclusion	0/0/3/16	0/0/1/9	0/0/2/7
Days in hospital before inclusion	2 ± 1	2 ± 1	1 ± 1
Dose of oral furosemide before hospitalization (mg)	80 [40–160]	100 [40–120]	80 [80–160]
Patient's self-reported weigh gain (kg)	8.6 ± 5.8	7.6 ± 6.3	9.8 ± 5.4
Heart rate at baseline (b.p.m.)	76 ± 15	75 ± 14	78 ± 17
Systolic blood pressure at admission (mmHg)	125 ± 14	128 ± 10	122 ± 18
Central venous pressure (mmHg)	15.5 ± 5.3	NA	15.5 ± 5.3
Central venous oxygen saturation (%)	49 ± 12	NA	49 ± 12
Left ventricular ejection fraction (%)	34 ± 15	34 ± 16	35 ± 15
Acute heart failure (*de novo*)	7 (37)	2 (20)	5 (55)
Ischaemic aetiology of heart failure	8 (42)	6 (60)	2 (22)
Haemoglobin (g/dL)	12.9 ± 1.3	13.2 ± 1.4	12.5 ± 1.2
White blood count (10^9/L)	6.7 ± 1.6	6.6 ± 1.5	6.9 ± 1.9
PLT (10^9/L)	164 ± 54	154 ± 41	177 ± 66
AST (IU/L)	32 ± 15	38 ± 17	25 ± 10
ALT (IU/L)	29 ± 21	38 ± 24	20 ± 12
Bilirubin (mg/dL)	1.6 ± 0.6	1.7 ± 0.7	1.5 ± 0.6
Sodium (mmol/L)	138 ± 4	139 ± 3	136 ± 4
Potassium (mmol/L)	4.1 ± 0.5	4.1 ± 0.4	4.0 ± 0.5
Serum osmolality (mmol/L)	277 ± 9	280 ± 8	274 ± 9
Creatinine (mg/dL)	1.45 ± 0.4	1.3 ± 0.4	1.6 ± 0.4
eGFR (mL/min/1.73 m^2)	58 ± 24	65 ± 28	51 ± 17
BUN (mg/dL)	33 ± 12	33 ± 12	34 ± 13
Albumin (mg/dL)	3.6 ± 0.4	3.6 ± 0.4	3.5 ± 0.3
NT-proBNP (pg/mL)	4492 [2662–6806]	4661 [2790–6584]	4303 [2635–5675]
UNa^+ at baseline (mmol/L)	70 ± 45 60 [35–83]	55 ± 22 50 [37–76]	85 ± 57 64 [35–144]
Length of hospital stay (days)	14 ± 9	14 ± 12	14 ± 5

Values are shown as *n* (%), mean ± standard deviation, or median [interquartile range].
AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; eGFR, estimated glomerular fitration rate; NA, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PLT, platelet; UNa^+, urine sodium.

Table 2 Diuresis, mean 0.9% NaCl solution infusion, net negative fluid balance and mean doses of furosemide during Reprieve therapy

Variable	Intervals of Reprieve therapy			
	(0–6 h)	(6–12 h)	(12–18 h)	(18 h–end of therapy)
TARGET-1				
Diuresis (mL/h)	351 ± 285	166 ± 104	88 ± 80	139 ± 160
0.9% NaCl infusion (mL/h)	251 ± 283	72 ± 87	40 ± 64	71 ± 120
Net negative fluid balance (mL/h)	100 ± 63	93 ± 59	47 ± 80	68 ± 68
Intravenous furosemide dose (mg)	48 ± 10	25 ± 13	14 ± 16	16 ± 21
Total furosemide dose (mg)	102 ± 43			
TARGET-2				
Diuresis (mL/h)	334 ± 204	270 ± 125	276 ± 134	222 ± 154
0.9% NaCl infusion (mL/h)	200 ± 191	133 ± 121	146 ± 109	103 ± 120
Net negative fluid balance (mL/h)	133 ± 55	137 ± 42	130 ± 57	119 ± 64
Intravenous furosemide dose (mg)	66 ± 15	63 ± 20	72 ± 35	68 ± 34
Total furosemide dose (mg)	262 ± 99			

Values are shown as mean ± standard deviation.

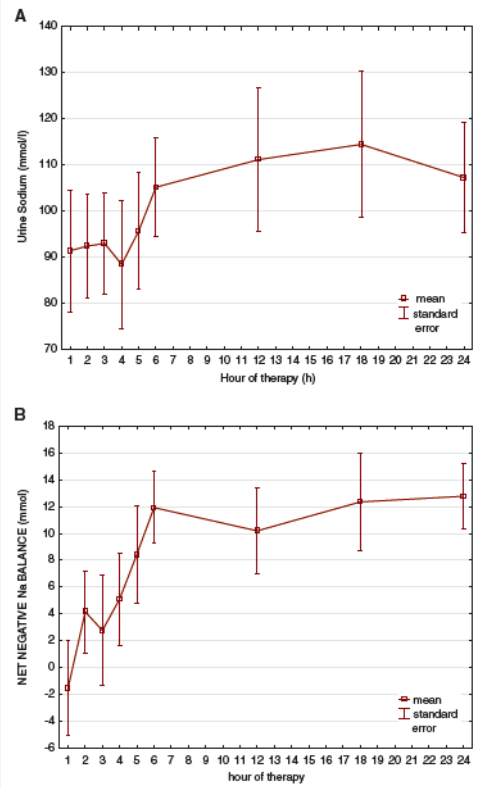

Figure 2 (*A*) Mean urine sodium concentration and (*B*) mean net negative sodium (Na) balance during Reprieve therapy in TARGET-2.

Urine and serum sodium during Reprieve therapy

Data on hourly UNa^+ concentration and sodium balance during the first 6 h of Reprieve therapy in the TARGET-2 population are shown in *Figure* 2. A trend toward a constant, gradual increase in UNa^+ within the first 6 h of treatment was observed. Mean UNa^+ at baseline was 91 ± 40 mmol/L and increased up to 105 ± 32 mmol/L after 6 h of treatment ($P = 0.15$), remaining stable at 12, 18 and 24 h (111 ± 44, 114 ± 44, 107 ± 36 mmol/L, respectively) (*Figure 2A*). Apart from the first hour of therapy, patients remained at net negative sodium balance during the treatment period (*Figure 2B*). The median sodium loss per hour was 9.7 [3–13] mmol/h.

Combined data from TARGET-1 and TARGET-2 showed a significant increase in mean serum sodium from 138 ± 4 mmol/L at baseline to 139 ± 4 mmol/L at 24 h ($P < 0.01$). The mean serum osmolality increased from 277 ± 9 mmol/L to 280 ± 8 mmol/L at the end of the procedure ($P = 0.02$).

Indices of renal function and laboratory parameters

We observed an improvement in renal function as evidenced by a decrease in creatinine (1.45 ± 0.4 mg/dL at baseline vs. 1.26 ± 0.4 mg/dL at the end of Reprieve therapy; $P < 0.001$) and plasma cystatin C levels (1.6 ± 0.6 mg/dL at baseline vs. 1.4 ± 0.6 mg/dL at the end of Reprieve therapy; $P < 0.05$). There was also a significant drop in serum urea nitrogen ($P < 0.001$). Moreover, the biomarkers of renal injury urine NGAL and serum KIM-1 remained stable during the treatment period (all $P > 0.05$) (*Table 3*).

Among all laboratory parameters assessed, a significant decrease was only observed in serum potassium level (from 4.1 ± 0.5 mmol/L at baseline to 3.6 ± 0.4 mmol/L at the end of therapy; $P < 0.01$). Blood gases and lactate levels remained unchanged.

Changes in clinical status during Reprieve therapy

All patients reported significant symptomatic improvement: PGA score decreased from 7.7 ± 1.1 points at baseline to 3.0 ± 1.3 points at the end of the procedure ($P < 0.001$) (*Table 4*). Jugular venous pressure and pulmonary congestion also improved significantly at the end of Reprieve therapy, whereas the magnitude of peripheral oedema did not change (*Table 4*). The median change in patients' weight during the procedure was −2.3 [−4.2; −1.6] kg. During hospital stay, patients' weight significantly decreased from 93.7 ± 21.6 kg at the start of therapy to 90.7 ± 07 kg at the end of therapy, and to 87.5 ± 16.9 kg at discharge (*Figure 3*). There was no change in NT-proBNP during Reprieve therapy ($P = 0.85$) (*Table 4*).

Haemodynamic monitoring

A decrease in CVP was observed (from 15.5 ± 5.3 mmHg at baseline to 12.8 ± 4.8 mmHg at the end of the Reprieve therapy; $P = 0.02$) (*Table 4*). In order to estimate cardiac output, central venous oxygen saturation was assessed, showing stable values during the treatment phase (49 ± 12% at baseline, 57 ± 8% at 6 h, and 54 ± 14% at 24 h; $P = 0.1$).

Discussion

This study demonstrates that the Reprieve System™ in conjunction with diuretic therapy supports safe and controlled decongestion in patients hospitalized with AHF. The primary efficacy endpoint to control actual fluid loss by matching it with planned target fluid loss was met in all study patients.

There are several aspects of the study that point toward new areas for investigation in the treatment of decongestion in AHF.

Decongestion remains the major goal of therapy in patients admitted with AHF, though there is no yet an established regimen for optimal use of diuretics in this clinical setting.[3–5] In everyday practice, physicians tend to use diuretics upon their experience,

Table 3 Markers of renal function and injury during Reprieve therapy

Renal markers	Baseline	12 h	End of Reprieve therapy	*P*-value
Serum creatinine (mg/dL)	1.45 ± 0.4	1.31 ± 0.4	1.26 ± 0.4	0.0002
Serum BUN (mg/dL)	33 ± 12	31 ± 8	30 ± 11	0.001
Plasma cystatin C (mg/dL)	1.6 ± 0.6	1.5 ± 0.5	1.4 ± 0.5	0.02
NGAL (ng/mL)	10.9 [7.4–26.9]	10.2 [4.8–17.1]	14.9 [7.1–25.6]	0.39
KIM-1 (pg/mL)	123.0 ± 58.1	114.9 ± 64.9	109.7 ± 59.7	0.36

Values are shown as mean ± standard deviation, or median [interquartile range].
BUN, blood urea nitrogen; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin.

Table 4 Comparison of clinical signs and laboratory indices of congestion at the start and at the end of Reprieve therapy ($n = 19$)

Variable	Start of Reprieve therapy	End of Reprieve therapy	*P*-value
Clinical signs of congestion			
Weight (kg)	93.7 ± 21.6	90.7 ± 20.7	<0.001
Jugular venous pressure (1–3 scale)			<0.05
1 (< 6 cm)	1/19	15/19	
2 (6–10 cm)	14/19	4/19	
3 (> 10 cm)	4/19	0/19	
Oedema (0–3 scale)			0.1
0	0/19	6/19	
1	8/19	4/19	
2	3/19	8/19	
3	8/19	1/19	
Pulmonary congestion (0–3 scale)			<0.05
0 (no rales)	0/19	11/19	
1 (rales <1/3 lung fields)	2/19	7/19	
2 (rales 1/3–2/3 lung fields)	16/19	1/19	
3 (rales >2/3 lung fields)	1/19	0/19	
Patient global assessment (points)	7.7 ± 1.1	3.0 ± 1.3	<0.0001
Central venous pressure (mmHg)	15.5 ± 5.3	12.8 ± 4.8	0.02
Laboratory indices of congestion			
NT-proBNP (pg/mL)	4492 [2662–6806]	4927 [3316–6250]	0.85
Serum osmolarity (mmol/L)	277 ± 9	280 ± 8	0.02
Sodium (mmol/L)	138 ± 4	139 ± 4	0.002

Values are shown as number of patients, mean ± standard deviation, or median [interquartile range].
NT-proBNP, N-terminal pro-B-type natriuretic peptide.

patient clinical profile and laboratory findings. There is reluctance to administer high doses of diuretics due to the risk for potential rapid, uncontrolled, intravascular volume depletion with all subsequent deleterious consequences.[4,8,14] This may lead to underdosing of diuretics with resultant ineffective decongestion. Additionally, decision on diuretic dose adjustment is often made with a substantial delay, typically several hours after initial diuretic administration. Our results show that the Reprieve System™ can improve these shortcomings. The Reprieve System™ allows real-time adjustment of fluid balance (net negative balance) during diuretic-based decongestion in patients with AHF, thus we have been able to control the effective volume being removed from an individual patient virtually at every moment during treatment. However, whether such an approach based on careful monitoring of hourly diuresis with concomitant adjustment of diuretics without the device would be equally efficient cannot be undeniably excluded. In both studies we met the efficacy endpoint of preventing excess fluid loss with fully controlled net volume removal. Of note, it follows our desired goal – in TARGET-1 smaller doses of furosemide were deliberately used as it was a safety/feasibility study, whereas in TARGET-2 furosemide doses were higher to promote/facilitate negative fluid balance.

Despite high rates of urine production during the entire period of Reprieve therapy, no signs of haemodynamic instability were seen. Mean blood pressure remained unchanged and there were no significant drops in systolic blood pressure in any patient. In those who underwent haemodynamic monitoring, we noticed a decrease in CVP (indicating effective decongestion) and a trend toward an

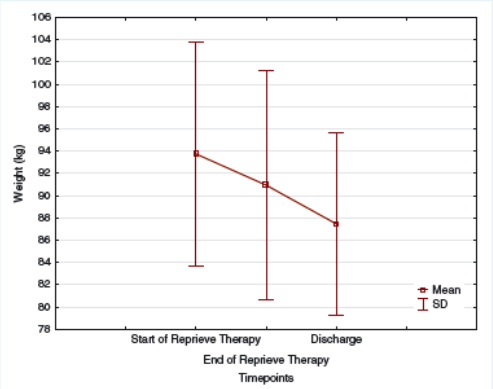

Figure 3 Patient's weight during hospitalization (start vs. end of Reprieve therapy, $P < 0.001$; discharge vs. end of Reprieve therapy, $P < 0.05$). SD, standard deviation.

increase in mixed venous oxygen saturation (as an indirect marker of preserved peripheral perfusion), accompanied by stable mean lactate level.[15–17] Again, we interpret these findings as an additional piece of evidence that controlled fluid removal with the Reprieve System™ is safe and associated with stabilization of haemodynamic status. This points out toward a need of 'smooth' decongestive therapies, which by preventing fast, uncontrolled removal of intravascular volume, would eliminate deleterious consequences of overdiuresis.

Sodium and water retention constitutes a major determinant of congestion in AHF. Therefore, effective decongestive therapy in the acute setting should aim at achieving a negative sodium and water balance (short-term) followed by longer-term reduction in extracellular fluid volume.[4] It has been demonstrated that vasopressin-2 receptor antagonists, which only increase free water elimination (aquaresis), are not effective in patients with AHF with respect to clinical outcomes.[18] In our study, all patients achieved net negative sodium balance. This was associated with net negative fluid balance accompanied by an increase in UNa^+ concentration during treatment. Indeed, we observed a trajectory of increasing natriuresis within the first 6 h of treatment, which seems to be an early prognosticator for effective diuretic response and decongestion and possibly better outcomes.[19,20] Moreover, we observed a significant increase of serum sodium and serum osmolality after 24 h of therapy, likely suggesting improvement of water/sodium handling, which is a well known factor of good prognosis in heart failure.[21] Hyponatraemia is often present in AHF, can be deteriorated by diuretics and may further attenuate diuretic response. Of note, the infusion of 0.9% NaCl (as a replacement) was relatively hypertonic if compared to patients' serum sodium concentration (mean serum sodium vs. infusion: 138 mmol/L vs. 153.9 mmol/L), which may also enhance diuretic effectiveness.

As previously mentioned, each patient experienced a significant (on average three-fold) increase in diuresis during Reprieve therapy. It should be stressed that this was associated with significantly higher doses of diuretics (vs. 24 h before and after therapy). The major concern of clinicians to use diuretics more 'aggressively' is renal function. However, in our cohort there was a hint of improvement of clinical signs of heart failure accompanied by improvement of renal function.

During the procedure, favourable changes in clinical signs and laboratory indices of congestion were observed. PGA and pulmonary congestion improved significantly, which was accompanied by a gradual decrease of CVP. Although NT-proBNP level remained unchanged after therapy, a 24 h period may not be long enough for natriuretic peptides to decrease.

There were no deaths, no serious adverse events, no infections, or other device and procedure-related complications. The most frequent adverse event was hypokalaemia, as mean serum potassium decreased from 4.1 mmol/L to 3.6 mmol/L ($P < 0.05$). Importantly, despite extensive urine production, no laboratory signs of acute kidney injury were seen, as biomarkers (KIM-1, NGAL) remained stable during and after therapy. Moreover, there was a significant improvement in markers of kidney function, as all creatinine, eGFR, blood urea nitrogen and plasma cystatin C improved significantly after Reprieve therapy. After Reprieve therapy termination, no rebound effect occurred in terms of weight or renal function, as patients lost approximately 6 kg and serum creatinine improved ~0.2 mg/dL till discharge.

It is worthnoting that Reprieve therapy is not any form of renal replacement therapy, we would rather call it a 'support' intervention, which means it needs (good enough) renal function to respond to diuretics. Thus, the effect of therapy depends on diuretic responsiveness, diuretic dose, Reprieve therapy itself, and set net negative volume. However, it allows clinicians to control the process of smooth decongestion.

In conclusion, the early data from the TARGET-1 and TARGET-2 trials support the hypothesis that Reprieve therapy enhances safe and controlled decongestion in AHF patients with preserved systolic blood pressure and pre-existing chronic renal disease, which is related to improvement of water/sodium handling and kidney function. These observations need further confirmation in larger cohorts of patients with AHF.

Study limitations

This was a single-centre, one-arm study, including a rather small population of predominantly male patients with AHF who showed relatively well-preserved haemodynamic status and most of whom were able to respond well to initial, standard diuretic therapy. Therefore, by design, patients that can be categorized as diuretic-resistant and can potentially benefit most from this treatment were excluded. However, one needs to remember this was an early feasibility study designed to evaluate treatment safety and accumulate data on device performance.

The study was not designed with a control group, and thus we cannot fully access the efficacy of therapy. The comparison of fluid loss before and during therapy may certainly be affected by a number of uncontrolled factors that may have impacted urine output and renal function before, during and after therapy. On the other hand, however, net negative fluid balance (particularly

in TARGET-2) was higher and whether this can be so efficiently achieved with adjustment of diuretic dosage (even applying recently recommended diuretic regimen),[22] without using the Reprieve System™, is not known and requires further evaluation in future studies.

As the diuretic regimen during the study was not controlled by any protocol, we need to be very cautious about conclusions on furosemide efficiency. Additionally, data on urine composition were available only during the period of Reprieve therapy, therefore we could not compare sodium excretion and balance before, during and after active treatment and no definite conclusions can be drawn regarding the effect of therapy on natriuresis.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Inclusion and exclusion criteria of the TARGET-1 and TARGET-2 studies.

Figure S1. Flowchart of the TARGET-1 and TARGET-2 studies.

Table S1. Diuresis, net fluid loss, furosemide doses 24 h before, during and 24 h after Reprieve therapy.

Conflict of interest: P.P. reports honoraria from RenalGuard Solution (speakers bureau and participation in clinical trial). J.T reports honoraria from RenalGuard Solution for consulting fees. J.B., R.Z., P.S., J.S., A.T., W.B. report honoraria from RenalGuard Solution for participation in clinical trial. A.H. and H.L. are employee of RenalGuard Solution.

References

1. Mullens W, Verbrugge FH, Nijst P, Tang WH. Renal sodium avidity in heart failure: from pathophysiology to treatment strategies. *Eur Heart J* 2017;**38**:1872–1882.
2. Nijst P, Verbrugge FH, Grieten L, Dupont M, Steels P, Tang WH, Mullens W. The pathophysiological role of interstitial sodium in heart failure. *J Am Coll Cardiol* 2015;**65**:378–388.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
4. Ellison DH, Felker GM. Diuretic treatment in heart failure. *N Engl J Med* 2017;**377**:1964–1975.
5. Ellison DH. Diuretic therapy and resistance in congestive heart failure. *Cardiology* 2001;**96**:132–143.
6. Voors AA, Davison BA, Teerlink JR, Felker GM, Cotter G, Filippatos G, Greenberg BH, Pang PS, Levin B, Hua TA, Severin T, Ponikowski P, Metra M; RELAX-AHF Investigators. Diuretic response in patients with acute decompensated heart failure: characteristics and clinical outcome – an analysis from RELAX-AHF. *Eur J Heart Fail* 2014;**16**:1230–1240.
7. ter Maaten JM, Dunning AM, Valente MA, Damman K, Ezekowitz JA, Califf RM, Starling RC, van der Meer P, O'Connor CM, Schulte PJ, Testani JM, Hernandez AF, Tang WH, Voors AA. Diuretic response in acute heart failure – an analysis from ASCEND-HF. *Am Heart J* 2015;**170**:313–321.e4.
8. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation* 2010;**122**:265–272.
9. Damman K, Kjekshus J, Wikstrand J, Cleland JG, Komajda M, Wedel H, Waagstein F, McMurray JJ. Loop diuretics, renal function and clinical outcome in patients with heart failure and reduced ejection fraction. *Eur J Heart Fail* 2016;**18**:328–336.
10. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, Maggioni AP, Cook T, Swedberg K, Burnett JC, Grinfeld L, Udelson JE, Zannad F, Gheorghiade M; EVEREST Trial Investigators. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J* 2013;**34**:835–843.
11. Marenzi G, Ferrari C, Marana I, Assanelli E, De Metrio M, Teruzzi G, Veglia F, Fabbiocchi F, Montorsi P, Bartorelli AL. Prevention of contrast nephropathy by furosemide with matched hydration. *JACC Cardiovasc Interv* 2012;**5**:90–97.
12. Mattathil S, Ghumman S, Weinerman J, Prasad A. Use of the RenalGuard system to prevent contrast-induced AKI: a meta-analysis. *J Interv Cardiol* 2017;**30**:480–487.
13. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999;**130**:461–470.
14. Damman K, Valente MA, Voors AA, O'Connor CM, Van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J* 2014;**35**:455–469.
15. Gallet R, Lellouche N, Mitchell-Heggs L, Bouhemad B, Bensaid A, Dubois-Randé JL, Gueret P, Lim P. Prognosis value of central venous oxygen saturation in acute decompensated heart failure. *Arch Cardiovasc Dis* 2012;**105**:5–12.
16. Zymliński R, Biegus J, Sokolski M, Siwołowski P, Nawrocka-Millward S, Todd J, Jankowska EA, Banasiak W, Cotter G, Cleland JG, Ponikowski P. Increased blood lactate is prevalent and identifies poor prognosis in patients with acute heart failure without overt peripheral hypoperfusion. *Eur J Heart Fail* 2018;**20**:1011–1018.
17. Biegus J, Zymliński R, Sokolski M, Gajewski P, Banasiak W, Ponikowski P. Clinical, respiratory, haemodynamic, and metabolic determinants of lactate in heart failure. *Kardiol Pol* 2018;**77**:47–52.
18. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST outcome trial. *JAMA* 2007;**297**:1319–1331.
19. Biegus J, Zymliński R, Sokolski M, Todd J, Cotter G, Metra M, Jankowska EA, Banasiak W, Ponikowski P. Serial assessment of spot urine sodium predicts effectiveness of decongestion and outcome in patients with acute heart failure. *Eur J Heart Fail* 2019;**21**:624–633.
20. Testani JM, Hanberg JS, Cheng S, Rao V, Onyebeke C, Laur O, Kula A, Chen M, Wilson FP, Darlington A, Bellumkonda L, Jacoby D, Tang WH, Parikh CR. Rapid and highly accurate prediction of poor loop diuretic natriuretic response in patients with heart failure. *Circ Heart Fail* 2016;**9**:1–8.
21. Matsue Y, Yoshioka K, Suzuki M, Torii S, Yamaguchi S, Fukamizu S, Ono Y, Fujii H, Kitai T, Nishioka T, Sugi K, Onishi Y, Noda M, Kagiyama N, Satoh Y, Yoshida K, Goldsmith SR. Prognostic importance of sodium level trajectory in acute heart failure. *Heart Vessels* 2017;**32**:1498–1505.
22. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, Testani JM, Tang WH, Orso F, Rossignol P, Metra M, Filippatos G, Seferovic PM, Ruschitzka F, Coats AJ. The use of diuretics in heart failure with congestion – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:137–155.

2. **Diuretic treatment using the RenalGuard® system in patients hospitalized due to acute decompensated heart failure and characterization of the profile of patients with good and poor response to treatment – preliminary study.**

   Paweł Siwołowski, Piotr Gajewski, Mateusz Sokolski, Robert Zymliński, Mateusz Guzik, Joanna Szachniewicz, Piotr Ponikowski; Cardiology Journal 2024, (*Ahead of print*) doi: 10.5603/cj.102386

Corresponding author:

Name Surname **Paweł Siwołowski**

Full institutional address (including street name and number and a postal code): **Department of Cardiology, Institute of Heart Diseases, University Hospital, Borowska 213, 50-556 Wroclaw, Poland**

Telephone number **+ 48 608378555**

Fax number (optional)

Email address**: patiks@yahoo.com**

Abstract.

Background. The aim of the study was to analyze the potential relationship between the diuretic response, the clinical profile and the concentrations of selected biochemical markers and to identify a group of patients who will benefit from a new form of therapy combining standard diuretic therapy with the use of a RenalGuard® system.

Methods. We investigated retrospectively 19 patients (mean age 67±10 years, 95% men) hospitalized due to ADHF (NYHA class III-IV, BP 125 ± 14 / 73 ± 16 mmHg, eGFR 58 ± 24) with persistent overhydration despite standard therapy. A targeted comparative analysis of selected clinical and biochemical parameters was performed to determine the parameters associated with a better diuretic response (good diuretic responders - GDR group).

Results. GDR group had significantly lower levels of creatinine (1.23 ± 0.4 vs. 1.69 ± 0.35, p 0.025) magnesium 0.70 ± 0.14 vs. 0.83 ± 0.09, p 0.030) and blood urea nitrogen (BUN, 28 ± 11 vs. 39 ± 10, p 0.045). Additionally, in GDR group a statistically significant greater ability to dilute urine in the 12th and 24th hour of therapy was found.

Conclusions. The results of the study indicate the potential use of the RenalGuard® system in combination with standard intravenous diuretic therapy for controlled dehydration in the treatment of a selected group of patients with ADHF. It is advisable to identify the detailed mechanisms of GDR and characterize this group of patients more precisely.

Keywords: acute heart failure, decongestion, diuretic response, spot urine analysis, biomarkers.

Introduction.

Despite the development of knowledge on heart failure pathogenesis and treatment, exacerbation of heart failure symptoms remains one of the main causes of hospitalization in hospital wards in patients over 65 years of age and is still related to high mortality and the frequency of rehospitalizations.[1] In-hospital mortality among patients hospitalized due to acute heart failure (AHF) ranges from 4 to 10%, and the incidence of death and re-hospitalization exceeds 45% in a one-year follow-up. The most common form of clinical manifestation in patients with acute heart failure (50-70% of cases) is the so-called acute decompensated heart failure (ADHF). Initial clinical evaluation of patients with decompensated heart failure allows for easy identification of four different hemodynamic profiles, including the largest group of patients with symptoms of overhydration, without reduced peripheral perfusion, i.e. the so-called "wet-warm" profile.[2]

Regardless of the cause of decompensation, one of the basic goals in treating patients with acute decompensated heart failure and symptoms of fluid overload is the rapid and safe elimination of overhydration using, among others, loop diuretics. It is known that excessive increase in the volume of the extravascular space is, alongside hyponatremia and increased blood urea nitrogen (BUN), one of the most important factors of poor prognosis in patients with decompensated heart failure. The associated chronic activation of many neurohormonal factors (mainly the renin-angiotensin-aldosterone system or vasopressin), in the group of patients treated for chronic heart failure, causes a gradual decrease in the effectiveness of standard pharmacological treatment, leading as a consequence to partial or complete resistance to diuretic treatment and progressive overhydration.

The first-line treatment option for exacerbation of chronic heart failure symptoms in patients with symptoms of congestion and overhydration remains loop diuretics, often in combination with vasodilators.[1],[3],[4],[5] The main goal of diuretic therapy is to remove excess fluid from the body. First, excess fluid is removed from the intravascular space and then a volume of fluid is moved from the extravascular space to the vessels of the vascular bed at a rate known as PRR - plasma refill rate. From a clinical point of view, the key element for the safety and effectiveness of diuretic therapy is the ability to achieve a stable, fully controlled rate of excess fluid movement from the extravascular space to the vascular bed. If the rate of excess fluid removal from the intravascular space is too fast in relation to the plasma refill rate, excessive emptying of the intravascular space may occur, resulting in a decrease in cardiac

output and decreased renal perfusion, which leads to the activation of a number of renal and extrarenal mechanisms of sodium and water retention in the body and, consequently, to the development of diuretic resistance.[6],[7] There are also no clear guidelines on the optimal dosing of diuretics, monitoring their efficacy and safety in terms of the risk of excessive diuretic effect (excessive dehydration), kidney damage and worsening of long-term prognosis. This is an extremely relevant clinical problem because deterioration of renal function during hospitalization due to exacerbation of heart failure symptoms is very common and has a significant impact on prognosis. As does chronic kidney disease coexisting with heart failure, which is an independent factor of poor prognosis in patients with acute heart failure. [8] Moreover, it should be considered that the use of furosemide in treatment of patients hospitalized in Intensive Care Units is associated with a significant risk of acute kidney damage.[9] There is therefore still a need to develop new, safe and effective methods for eliminating overhydration and monitoring diuretic therapy in patients with acute heart failure.

Aim of the study.

The aim of the study was to assess the use of a loop diuretic (furosemide) in combination with the method of controlled dehydration using the RenalGuard® system in patients with ADHF and concomitant chronic kidney disease, hospitalized due to ADHF, and to attempt to identify a group of patients who will derive significantly greater benefit from this form of therapy, based on the analysis of the potential relationship between the diuretic response and the clinical profile of these patients and the concentrations of selected biochemical markers.

Methods.

The analysis was performed based on a prospective, single-center study conducted in patients hospitalized in the 4th Military Clinical Hospital in Wrocław due to ADHF.

The study involved a non-randomized, retrospective analysis of the therapy of 19 patients hospitalized due to ADHF (NYHA class III-IV, BP 125 ± 14 / 73 ± 16 mmHg, eGFR 58 ± 24) with persistent symptoms of overhydration despite standard therapy based on the use of an intravenous loop diuretic. The study was conducted with the approval of the local Bioethics Committee of the Lower Silesian Chamber of Physicians and the Bioethics Committee at the Medical University of Wrocław (opinion No. KB – 210/2019) and in

accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. All patients gave their written informed consent to participate in the study before being included in the study.

The most important inclusion criteria for the study included:

1. primary diagnosis of acute heart failure as the cause of hospitalization

2. clinical signs of overhydration (despite standard treatment of acute heart failure with intravenous furosemide), which included: persistent dyspnea at rest or with minimal physical effort at screening and recruitment, basal crackles, peripheral edema ≥ +1 (on a scale 0-3 +) on physical examination and radiological evidence of pulmonary congestion on plane chest X-ray.

3. elevated natriuretic peptide levels: BNP (B-type natriuretic peptide) ≥ 500 pg/mL or NT-proBNP (N-terminal pro-B-type natriuretic peptide) ≥ 2000 pg/mL; in patients ≥ 75 years of age or with current atrial fibrillation (at the time of inclusion), BNP ≥ 750 pg/mL or NT-proBNP ≥ 3000 pg/mL.

4. systolic blood pressure ≥100 mmHg at the start and end of the screening test

5. previous chronic kidney disease defined as an estimated glomerular filtration rate (eGFR) between presentation and enrollment to the study ≥25 and <90 mL/min/1.73 m2, calculated using the MDRD equation.

The exclusion criteria included mainly:

1. Total urine output < 200 ml or average urine rate < 50 ml/hour in the Diuretic Challenge.
2. Patient is managed on, or there is a plan to manage on, renal replacement therapy (RRT) such as ultrafiltration, hemofiltration or dialysis.
3. Dyspnea due to non-cardiac causes, such as acute or chronic respiratory disorders or infections (i.e., severe chronic obstructive pulmonary disease, bronchitis, pneumonia), which may interfere with the ability to interpret the primary cause of dyspnea.
4. Patients with blood pressure > 180 mmHg at the time of enrollment or persistent heart rate > 130 bpm.
5. Significant, uncorrected, left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy or severe aortic or mitral stenosis.

The intravenous administration of a loop diuretic recommended by the current ESC guidelines in the treatment of patients with acute heart failure was combined with the use of the RenalGuard® system, which operates by administering 0.9% saline solution by intravenous infusion in an amount proportional to the continuously measured volume of urine obtained per hour. The loop diuretic (furosemide) was administered in an individual dose for each patient, determined by the treating physician, necessary to ensure a time-planned negative fluid balance value.

Patients treated with intravenous furosemide during the first 24 hours of hospitalization, underwent a therapy combining intravenous furosemide with the use of the RenalGuard® system and the Fluid Loss Limit (FLL) determined by the treating physician for the next 24 hours. The RenalGuard® system infusion catheter was connected to the patient via a peripheral venous access, and a urine reservoir placed on the device scale was connected to a standard Foley catheter placed in the patient's bladder for continuous monitoring of urine output. At the beginning of therapy, all patients received 40mg of furosemide as an intravenous bolus. In the first hour of therapy, hydration was continued in a 1:1 ratio to the obtained diuretic effect (Matched Fluid Balance phase), and then the desired fluid balance was set (Desired Fluid Balance phase) at -100ml/h. (Figure 1A,1B) Subsequent doses of furosemide and the drug administration regimen (intravenous bolus or continuous intravenous infusion) were determined based on the assessment of the patient's clinical condition in order to achieve the assumed negative fluid balance. The study lasted up to 24 hours or until the assumed fluid loss was achieved, indicating the achievement of euvolemia, as assessed by the study doctor. In all patients, the symptoms of heart failure and diuretic effect were assessed, blood and urine were collected for laboratory assessment of selected biochemical parameters and biomarkers such as creatinine, eGFR, cystatin C, NGAL, ET-1, KIM-1 at specific time intervals during therapy, at discharge and during 30-day follow-up, as well as the relationship between the diuretic response and the sodium ions and creatinine levels in urine.

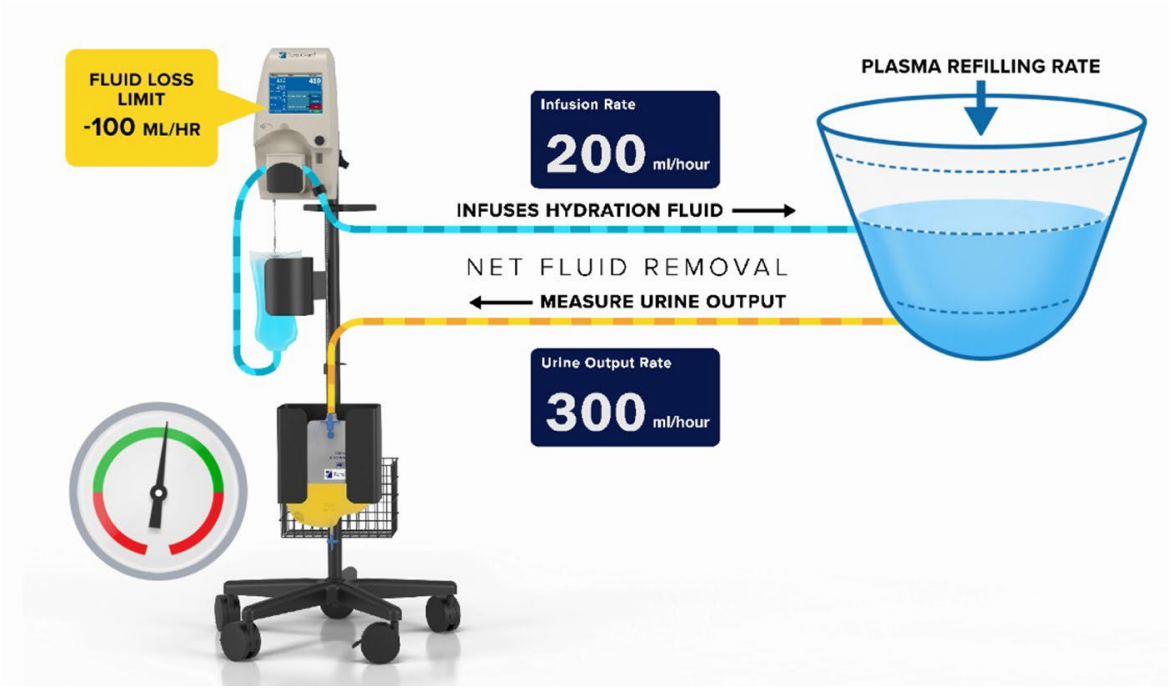

Figure 1A. Diagram of the RenalGuard® system.

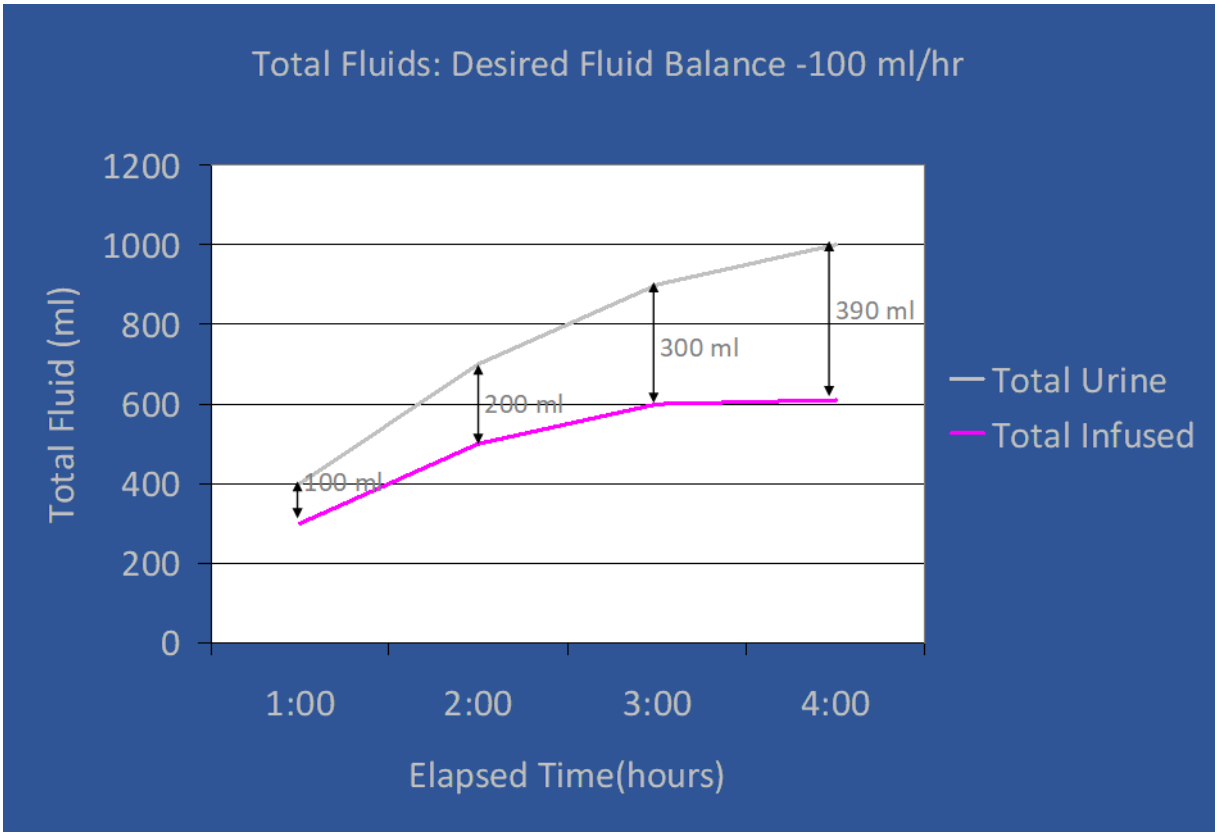

Figure 1B Diagram of the RenalGuard® system.

Statistical analysis.

Normally distributed continuous variables were described by means ± standard deviation, non-normally distributed variables were described by medians with [upper and lower quartiles], categorical variables were given as counts and percentages. The normality of the distribution was tested using the Shapiro-Wilk test. The statistical significance of differences between time points was assessed using the paired samples t test or the Wilcoxon test. Differences between the good and poor diuretic response groups were assessed using the unpaired t test or the Mann-Whitney test. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using STATISTICA 13 software (StatSoft Poland, Kraków, Poland).

Results.

The clinical characteristics of the study population are summarized in Table 1. The vast majority of the study group were men (95%), the mean age was 67 ± 10 years. Immediately before enrollment to the study, 16 patients (84%) presented with symptoms of heart failure in NYHA class IV, the remaining patients were in NYHA class III. The mean systolic blood pressure on admission was 125 ± 14 mmHg, NTproBNP level was 4492 [2662 – 6806] pg/mL, and hospitalization time 14 ± 9 days.

Variable		Good diur resp	Worse diur resp.	p
Patients, n	19	0	9	
Age, years	67±10	66±13	69±7	0.806
Male sex, n (%)	18 (95)	9 (90)	9 (100)	0.48
NYHA class I/II/III/**IV** before inclusion	0/0/3/**16**	0/0/1/**9**	0/0/2/**7**	0.465
Left ventricular ejection fraction (%)	34±15	32±13	37±17	0.743
Acute heart failure de novo (%)	8 (42)	3(30)	5(55)	0.259
Ischaemic aetiology of heart failure (%)	8 (42)	6(60)	2(22)	0.958
Days in hospital before inclusion	2±1			
LOS (days)	14±9.4	12.6±9.3	15.7±9.9	0.391
Signs and symptoms				
Patient's self-reported weigh gain (kg)	8.6±5.8			
Congestion at admission <1/3 **/** 1/3-2/3 **/** >2/3 (%)	2 (11) / 16 (84) / 1 (5)			
Peripheral oedema + / ++ / +++ (%)	8 (42) / 3 (16) / 8 (42)			
JVP <6 / 6-12 / >12 (cm)	1 (5) / 14 (74) / 4 (21)			
Heart rate at baseline (b.p.m.)	76±15	74±15	78±16	0.713
Systolic blood pressure at admission (mmHg)	125±14	125±11	125±18	0.967
Central venous oxygen saturation (%)	49±12			
Treatment before admission				
Furosemide dose before hospitalisation, mg	80 [40-160]			
Baseline laboratory parameters				
Haemoglobin (g/dL)	12.9±1.3	13.1±1.56	12.6±1.08	0.513
White blood count (10^9/L)	6.7±1.6	6.8±1.33	6.7±2.01	1.000
PLT (10^9/L)	164±54	170±54	159±57	0.838
AST (IU/L)	32±15	34±16	30±14	0.595
ALT (IU/L)	29±21	33±24	25±17	0.743
Bilirubin (mg/dL)	1.6±0.6	1.5±0.5	1.7±0.7	0.513
Albumin (mg/dL)	3.6±0.4	3.5±0.4	3.6±0.3	0.462
Sodium (mmol/L)	138±4	138±3.7	137±4.3	0.870
Potassium (mmol/L)	4.1±0.5	4.1±0.5	4.0±0.4	0.653
Serum osmolality (mmol/L)	277±9			
Creatinine (mg/dL)	1.45±0.4	1.23±0.4	1.69±0.35	**0.025**
eGFR baseline (mL/min/1.73 m2)	57±23	68±25	47±14	0.079

BUN (mg/dL)	33±12	28±11	39±10	**0.045**
NTproBNP (pg/mL)	4492 [2662-5806]	3684 [2635-5624]	5389 [4695-6448]	0.066
Urine sodium (mmol/l)	70±45	73±43	66±49	0.563
Urine chloride (mmol/l)	88±32	103±32	72±24	0.120
Urine creatinine (mg/dl)	98±54	120±55	73±43	0.230

Table 1 - Clinical characteristics of the population.

Diuretic effect

The mean duration of the Renal Guard® therapy in the analyzed group of patients was 25 ± 1 hours. The diuretic response during therapy expressed in milliliters [mL] was assessed per 40 mg of furosemide, obtaining a median for the entire study population of 933mL/40mg. (Table 2)

	Diuretic response during therapy based on 40 mg of furosemide					
	Nvalid	Mean	Median	Lower quartile	Upper quartile	Std dev.
Diuretic response ml/40mg	19	1043,860	933,3333	700,0000	1400,000	508,3625

Table 2 – Diuretic response during therapy (per 40 mg of furosemide).

Based on the median obtained in this way, the study population was divided into two groups:

1. Those patients who achieved a better diuretic effect and clinical response during the therapy were called "good diuretic responders" (GDR)

2. Those patients who achieved a worse diuretic effect and had less benefit from the therapy were called "worse diuretic responders" (WDR). (Table 3)

Variable	Two groups based on the median for the entire population: 933 ml/40 mg						
	Good diuretic response 1	Nvalid	Mean	Median	Lower quartile	Upper quartile	Std dev.
Good Diuretic Resposne ml/40mg	1,00	9	1448,148	1400,000	1066,667	1900,000	426,2599
Worse Diuretic Resposne ml/40mg	0,00	10	680,0000	725,0000	600,0000	800,0000	211,6659

Table 3 - Two groups based on the median for the entire population: 933 ml/40 mg.

Biochemical parameters

In the next stage, a targeted comparative analysis of selected clinical and biochemical parameters was performed for the first time in both groups to determine in detail the parameters associated with a better diuretic response and the greatest clinical benefit after the applied therapy. In the good diuretic responders (GDR) group, significantly lower levels of creatinine, magnesium and blood urea nitrogen (BUN) were found. (Table 4)

Variable	Good diuretic response GDR	Worse diuretic response WDR	P
Creatinine (mg/dl)	1.23 ± 0.4	1.69 ± 0.35	**0.025**
BUN (mg/dl)	28 ± 11	39 ± 10	**0.045**
Magnesium (mg/dl)	0.70 ± 0.14	0.83 ± 0.09	**0.030**
Cystatin C (mg/dl)	1.36 ± 0.5	1.85 ± 0.6	0.112
NGAL (ng/ml)	21.38 ± 17.16	19.61 ± 21.81	0.755
ET-1 (pg/ml)	13.97 ± 9.77	71.02 ± 169.25	0.134
KIM-1 (pg/ml)	140.67 ± 25.45	1177.25 ± 2716.97	0.404

Table 4 - Biochemical parameters – comparison

Moreover, the analysis of electrolyte levels in spot urine samples collected at specific time intervals of therapy revealed no significant differences of sodium and chloride ions concentrations at the beginning, in the 1st, 6th, 12th hour and after the end of therapy. (Figure 2)

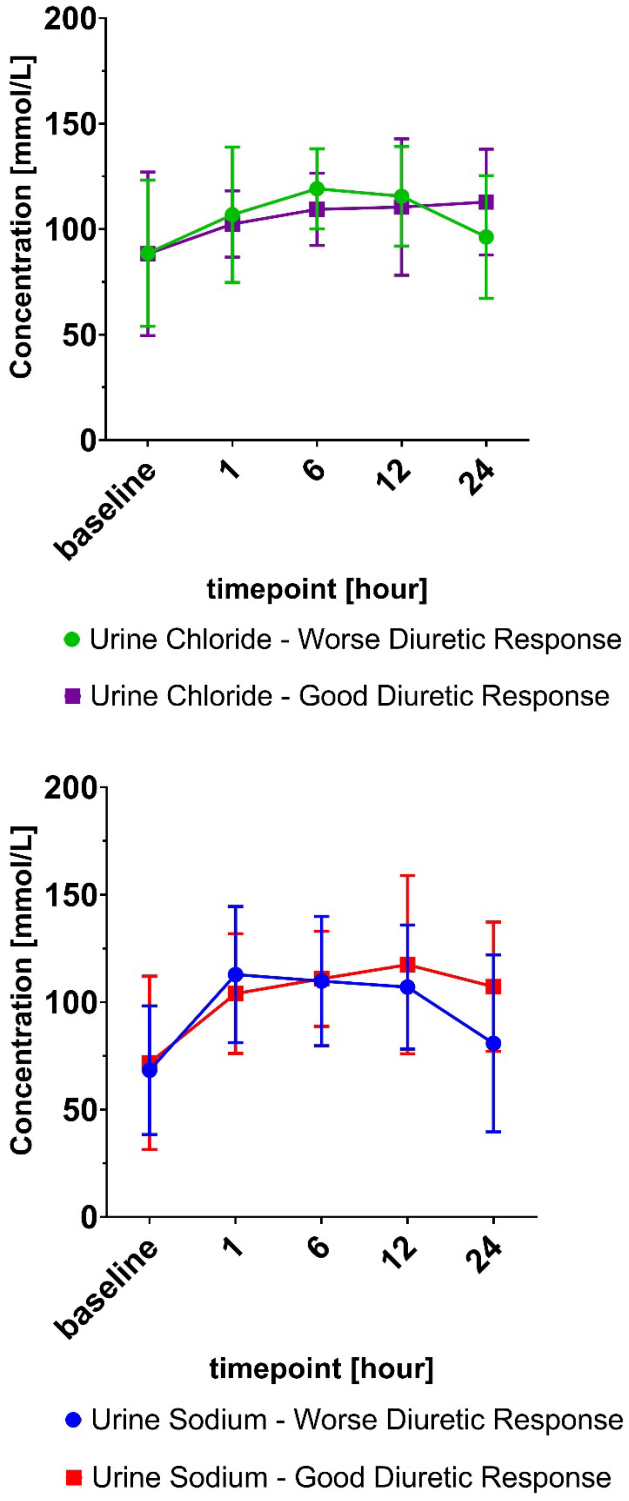

Figure 2 – Sodium and chloride urine concentration.

The relationships between the diuretic response and the concentrations of sodium ions and creatinine in urine used as markers of the kidney's ability to dilute urine (uCreat in baseline to uCreat in subsequent timepoints) and the relationships between natriuresis and urine dilution

(water excretion) defined as uNa/uCreat were also analyzed in the studied patient population. In the "good diuretic responders" (GDR) group, a statistically significant greater ability to dilute urine was found in the 12th and 24th hour of therapy, with no differences in uNa/uCreat concentration values. (Figure 3)

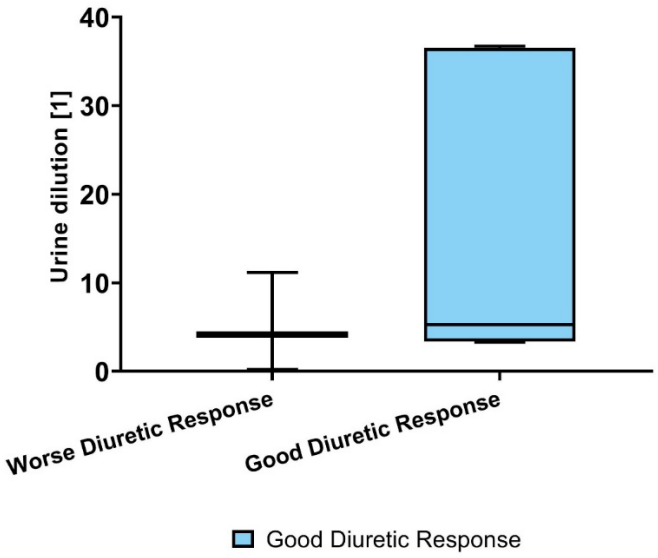

Figure 3A. Urine dilution 1h.

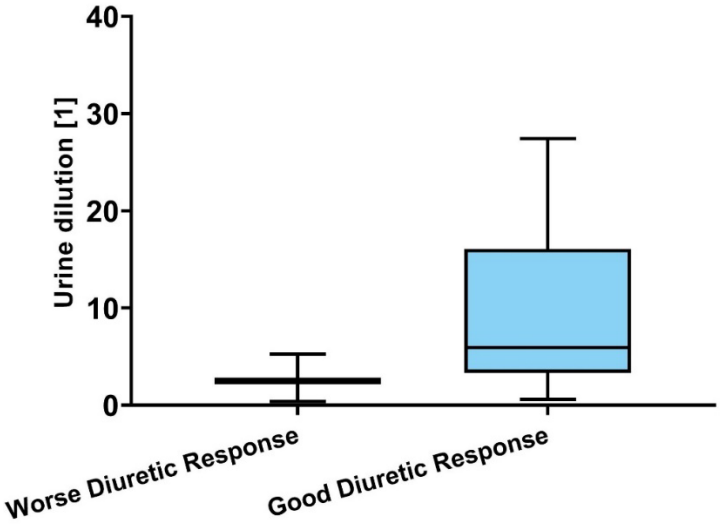

Figure 3B. Urine dilution 6h.

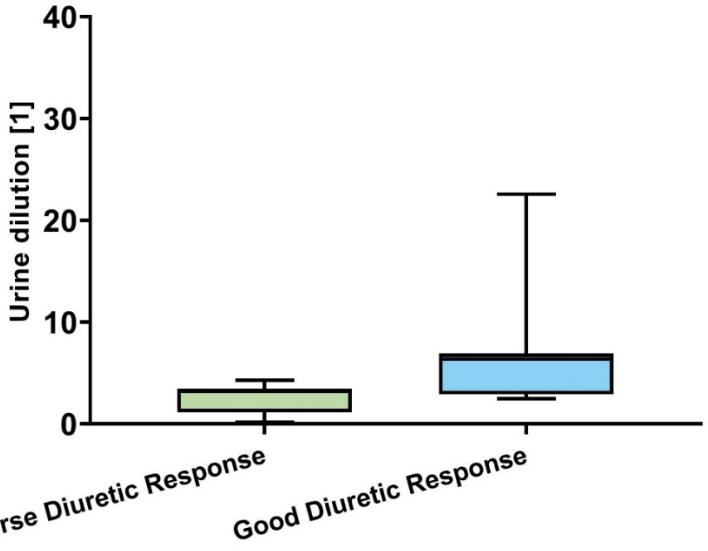

Figure 3C. Urine dilution 12h.

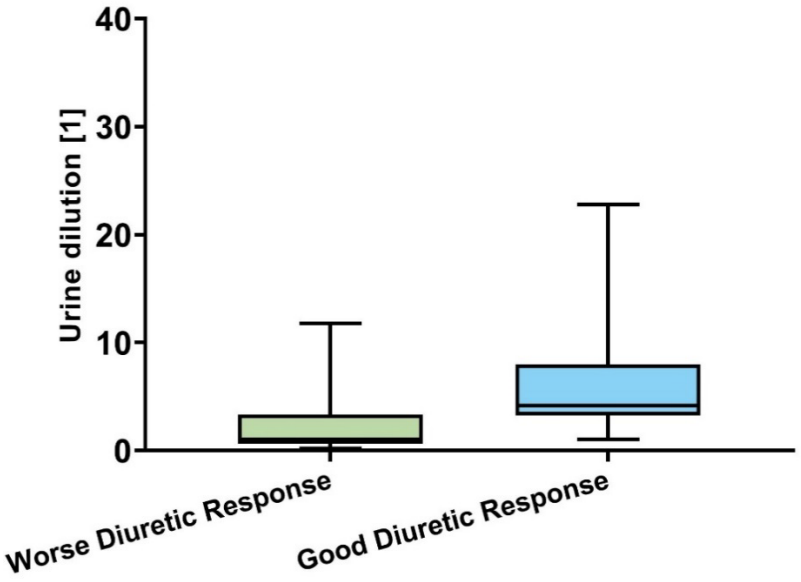

Figure 3D. Urine dilution 24h.

It is also worth noting the significantly lower total dose of the loop diuretic used to achieve the expected diuretic effect. In the assessment of clinical symptoms, patients from the "good diuretic responders" (GDR) group were characterized by less severe symptoms of overhydration, such as jugular venous pressure (JVP), pulmonary congestion or peripheral edema. (Figure 4)

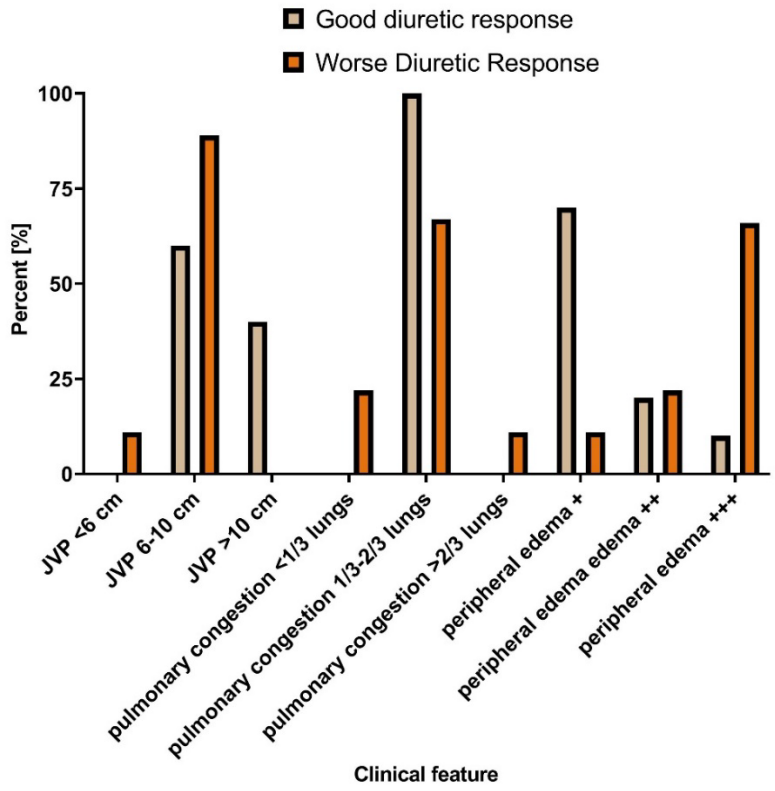

Figure 4. Clinical feature.

Discussion.

Overhydration, with or without signs of hypoperfusion, is a major cause of hospitalization in patients with ADHF, regardless of the geographic region.[10] From a historical point of view, the first alternative method of dehydration to loop diuretics in patients with ADHF and signs of overhydration was continuous venovenous ultrafiltration.[11],[12] The randomized UNLOAD trial, which evaluated the clinical effect of ultrafiltration versus standard diuretic therapy in the treatment of acute heart failure, demonstrated greater net weight loss and fluid loss within 48 hours and a lower rate of rehospitalization due to heart failure symptoms at a 90-day follow-up.[13] In contrast to previous clinical trials, a study published in 2012 highlighted for the first time a significant limitation of the use of this method, namely the risk of exacerbation of chronic kidney disease in a group of patients treated with ultrafiltration who had a significant increase in urea nitrogen and creatinine levels.[14] In the study by Vazir et al., the saturation of central venous blood was analyzed during ultrafiltration and an increase in venous oxygen tension and a decrease in creatinine concentration were observed in the first phase of dehydration. After obtaining 2 liters of removed fluid volume, a decrease in CVO2 and deterioration of renal function were noted. The authors of the study suggest that the

deterioration of renal function may be related to transient changes in cardiac output occurring during ultrafiltration.[15] The above observation may be of significant importance in the context of the safety of controlled dehydration using the RenalGuard system, because in the study group there was no significant variability of CVO2 during the therapy; 49±12% at baseline, 57±8% after 6 hours and 54±14% after 24 hours (p=0.1).

So far, a number of clinical trials have been conducted using the Renal Guard system, proving its efficacy in preventing post-contrast nephropathy, including in the group of patients with chronic kidney disease undergoing urgent or planned percutaneous coronary revascularization procedures.[16],[17],[18],[19] Based on a previously conducted analysis of the safety and efficacy of the RenalGuard system in treating patients with ADHF, the procedure was well tolerated and none of the patients had any infections or other complications related to the procedure, either during or after the treatment phase. All patients noted significant improvement in heart failure symptoms. The primary efficacy endpoint in preventing excessive fluid loss – actual fluid loss not exceeding the target fluid loss after completion of Renal Guard therapy – was met in all 19 (100%) patients. During the 30-day follow-up, no deaths or serious adverse events were reported in the study population. Maintaining venous volume expansion and renal perfusion pressure may have additional nephroprotective effects.[20]

The authors of a consensus statement by the Heart Failure Association of the European Society of Cardiology published in 2021 drew attention to the need to profile patients with heart failure in the context of making therapeutic decisions depending on the coexistence of factors such as heart rate (below 60 bpm or above 70 bpm, atrial fibrillation, symptomatic hypotension, eGFR below 30 or above 30 mL/min, hyperkalemia and clinical symptoms of overhydration. [21] Currently, many authors also emphasize the role of sodium and chloride ions in the pathophysiology of water and electrolyte metabolism disorders in the course of acute heart failure and the assessment of their concentrations in spot urine samples as predictors of response to diuretic therapy and independent factors allowing the identification of high-risk patients in the course of ADHF episodes. [22],[23],[24],[25] Researchers are also focusing on explaining the interrelationship between urinary sodium and creatinine concentrations and the response to standard diuretic therapy, which is measured by the ability to dilute urine. [26],[27] In the analyzed population, a significantly greater ability to dilute urine was found in the group of patients who were characterized by a better diuretic response (GDR).

It is interesting to note that higher urinary sodium concentrations were observed between groups at subsequent time points, in the group with a better overall diuretic response, but no significant

differences were found when the correlation between natriuresis and urine dilution (sodium concentration corrected for urine creatinine concentration) was taken into account, which is consistent with the fact that natriuresis is a strong factor determining the diuretic response. Patients with a better diuretic response showed a greater ability to dilute urine at later time points (>12 hours) despite the same natriuresis. Despite differences in diuretic response, no significant differences were found in the serum concentrations of renal damage markers such as Cystatin or Kim-1. However, a trend towards higher endothelin concentrations was observed at subsequent time points in patients with better response to treatment, which may support increased activation of this system as a compensatory mechanism in response to increased urine production by the kidneys (fluid loss).

Conclusions.

The results of the study indicate the potential use of the RenalGuard system in the treatment of a selected group of patients with ADHF and symptoms of overhydration, in combination with standard intravenous diuretic therapy for controlled dehydration. Based on the analysis of selected biochemical parameters, a correlation was demonstrated between the concentrations of creatinine, urea nitrogen (BUN), magnesium in serum and the diuretic response of patients undergoing therapy with the RenalGuard system. Some differences in sodium and chloride ions concentrations in urine samples collected at specific time intervals were also observed, but they were statistically insignificant. Limitations of the study resulting from the small size of the study population, single-center cohort and retrospective analysis prevented precise determination of the clinical profile of the group of patients with ADHF who could be expected to have a good diuretic response without an increased risk of glomerular filtration deterioration secondary to concomitant chronic kidney disease.

Further work to determine the precise hemodynamic and biochemical profile of a larger population of patients with the optimal effect after this form of therapy may improve the future efficacy and safety of renal replacement therapies, currently widely used in cardiac intensive care units in patients treated for ADHF.

References.

1. McDonagh T.A. et al.: “2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure” European Heart Journal (2021), Volume 42, Issue 36, 3599–3726. https://doi.org/10.1093/eurheartj/ehab368

2. Shah M.R. et al.:" Hemodynamic profiles of advanced heart failure: association with clinical characteristics and long-term outcome." Journal of heart failure 2001, Volume 7(2); 105-113.
3. Mentz R.J. et al.: "Decongestion in acute heart failure" European Journal of Heart Failure (2014) 16, 471–482.
4. Mullens W. et al.: "The use of diuretics in heart failure with congestion – a position statement from the heart failure association of the European Society of Cardiology" European Heart Journal (2019), Volume 21(2); 137-155
5. Filippatos G. et al.: "Global differences in characteristics, precipitants, and initial management of patients presenting with acute heart failure" JAMA Cardiol. 2020;5(4):401-410
6. Cleland JGF et al. Practical Applications of Intravenous Diuretic Therapy in Decompensated Heart Failure The American Journal of Medicine 2006;119;12;26-36
7. Cox Z.L. et al.: "Compensatory post-diuretic renal sodium reabsorption is not a dominant mechanism of diuretic resistance in acute heart failure" Eur Heart Journal 2021 Volume 42(43):4468-4477
8. Verdani V. et al.: "Worsening Renal Function in Patients Hospitalized with Acute Heart Failure: Risk Factors and Prognostic Significances" International Journal of Nephrology Volume 2011, Article ID 785974, 5 pages doi:10.4061/2011/785974
9. Levi T.M. et al.: "Furosemide is associated with acute kidney injury in critically ill patients" Braz J Med Biol Res, September 2012, Volume 45(9):827-833
10. Chioncel O. et al.: "Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry." European Journal of Heart Failure, 2017 Volume 19(20):1242-1254.
11. Costanzo M.R. et al.: "Early ultrafiltration in patients with decompensated heart failure and diuretic resistance. J Am Coll Cardiol 2005;46:2047–51.
12. Bart B.A., Boyle A, Bank AJ, et al. Ultrafiltration versus usual care for hospitalized patients with heart failure: the relief for acutely fluidoverloaded patients with decompensated congestive heart failure (RAPID-CHF) trial. J Am Coll Cardiol 2005;46:2043– 6.
13. Constanzo M.R. et al.: "Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure." J Am Coll Cardiol. 2007 Feb 13;49(6):675-83. Epub 2007 Jan 26.
14. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, Ofili EO, Stevenson LW, Semigran MJ, Felker GM, Chen HH, Hernandez AF, Anstrom KJ, McNulty SE, Velazquez EJ, Ibarra JC, Mascette AM, Braunwald E; Heart Failure Clinical Research Network: Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med 2012;367:2296–2304.
15. Vazir A, Simpkin VL, Marino P, Ludman A, Banya W, Tavazzi G, Bastin AJ, Trenfield S, Ghori A, Alexander PD, Griffiths M, Price S, Sharma R, Cowie MR: Association of haemodynamic

changes measured by serial central venous saturation during ultrafiltration for acutely decompensated heart failure with diuretic resistance and change in renal function. Int J Cardiol 2016;220:618–622.

16. Briguori C. et al.: "Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II): RenalGuard System in high-risk patients for contrast-induced acute kidney injury." Circulation. 2011 Sep 13;124(11):1260-9. doi: 10.1161/CIRCULATIONAHA.111.030759. Epub 2011 Aug 15.
17. Marenzi G. et al.: "Prevention of contrast nephropathy by furosemide with matched hydration: the MYTHOS (Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention) trial." JACC Cardiovasc Interv. 2012 Jan;5(1):90-7. doi: 10.1016/j.jcin.2011.08.017
18. Mattathil S, Ghumman S, Weinerman J, Prasad A. "Use of the RenalGuard system to prevent contrast-induced AKI: A meta-analysis." *Journal of Interventional Cardiology* 2017;30:480–487.
19. Luckraz H. et al.: „Reduction in acute kidney injury post cardiac surgery using balanced forced diuresis: a randomized, controlled trial." European Journal of Cardio-Thoracic Surgery 59 (2021) 562–569 doi:10.1093/ejcts/ezaa395
20. Biegus J. et al.: "Controlled decongestion by Reprieve therapy in acute heart failure: results of the TARGET-1 and TARGET-2 studies." Eur J Heart Fail. 2019 Sep;21(9):1079-1087. doi: 10.1002/ejhf.1533. Epub 2019 Aug 29.
21. Rosano G. et al.: „Patient profiling in heart failure for tailoring medical therapy. A consensus document of the HFA of the ESC" Eur J Heart Fail. 2021 Jun;23(6):872-881
22. Zandijk A.J.L et al.: „Chloride in heart failure. The neglected electrolyte." J Am Coll Cardiol HF 2021;9:904-915
23. Kataoka H. et al.: "Chloride in heart failure syndrome: its pathophysiologic role and therapeutic implication." Cardiol Ther (2021);10:407-428
24. Biegus J. et al.: "Renal profiling based on estimated glomerular filtration rate and spot urine sodium identifies high-risk acute heart failure patients." Eur J Heart Failure 2021;23(5):729-739
25. Nawrocka-Millward S. et al.: „The role of urine chloride in acute heart failure". Scientific Reports 14, 14100 (2024). https://doi.org/10.1038/s41598-024-64747-5
26. Iwanek G. et al.: "Spot urine sodium-to-creatinine ratio surpasses sodium in identifying poor diuretic response in acute heart failure." ESC Heart Failure (2024) Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/ehf2.14883
27. Guzik M. et al.: "Spot urine sodium as a marker of urine dilution and decongestive abilities in acute heart failure." Scientific Reports (2024) 14:1494 DOI:10.1038/s41598-024-51744-x

PODSUMOWANIE I WNIOSKI

Wg raportu OECD (Organizacji Współpracy Gospodarczej i Rozwoju) wartość wskaźnika liczby hospitalizacji z powodu niewydolności serca w Polsce w przeliczeniu na liczbę mieszkańców jest bez mała 3 krotnie wyższa niż średnia dla pozostałych krajów europejskich[14]. Główną przyczyną hospitalizacji pacjentów z ostrą dekompensacją niewydolności serca, niezależnie od regionu geograficznego, jest przewodnienie z objawami hipoperfuzji lub bez hipoperfuzji[15]. Stąd wynika potrzeba opracowania bezpiecznej metody efektywnego odwadniania oraz monitorowania efektu diuretycznego u chorych hospitalizowanych z powodu ostrej dekompensacji niewydolności serca, zwłaszcza tych obarczonych istotnym ryzykiem ostrego uszkodzenia nerek.

Pierwszą, alternatywną dla diuretyków pętlowych, metodą odwadniania u chorych z dekompensacją niewydolności serca i cechami przewodnienia, którą oceniano w badaniach klinicznych była ciągła żylno-żylna ultrafiltracja[16,17]. W randomizowanym badaniu UNLOAD oceniającym efekt kliniczny zastosowania ultrafiltracji w porównaniu ze standardową terapią diuretyczną w leczeniu ostrej niewydolności serca wykazano większą utratę wagi oraz płynu netto w ciągu 48 godzin, a także mniejszą częstość rehospitalizacji z powodu objawów niewydolności serca w obserwacji 90-dniowej[18]. W kolejnych próbach klinicznych zwrócono jednak uwagę na istotne ograniczenie zastosowania tej metody poprzez ryzyko zaostrzenia przewlekłej choroby nerek w grupie pacjentów leczonych za pomocą ultrafiltracji, u których stwierdzono istotny wzrost stężenia azotu mocznika i kreatyniny[19,20].

Dotychczas przeprowadzono szereg badań klinicznych z zastosowaniem systemu Renal Guard® w których udowodniono jego skuteczność w profilaktyce nefropatii pokontrastowej, między innymi w grupie pacjentów z przewlekłą chorobą nerek poddawanych pilnym lub planowym zabiegom przezskórnej rewaskularyzacji wieńcowej[21-24].

Na podstawie badań przeprowadzonych w ramach niniejszej rozprawy po raz pierwszy wykazano, że zastosowanie standardowej terapii diuretykiem pętlowym (furosemid) w połączeniu z systemem RenalGuard® w leczeniu ostrej niewydolności serca daje możliwość skutecznego i bezpiecznego, kontrolowanego odwadniania pacjentów hospitalizowanych z powodu ostrej dekompensacji niewydolności serca z objawami przewodnienia. Procedura była dobrze tolerowana, żaden z pacjentów nie miał infekcji ani innych powikłań związanych z

procedurą, zarówno w czasie jej trwania jak i po fazie leczenia. Podczas całego okresu leczenia skurczowe ciśnienie krwi pozostawało stabilne (123 ± 24 mmHg na początku, 115 ± 24 mmHg po 6 godzinach, 119 ± 19 mmHg po 12 godzinach i 116 ± 20 mmHg na końcu terapii Renal Guard®; p = 0,19). Wszyscy pacjenci odnotowali istotną poprawę objawów niewydolności serca. W 30-dniowej obserwacji nie odnotowano zgonów ani poważnych zdarzeń niepożądanych w badanej populacji. Stabilne stężenia parametrów uszkodzenia nerek odnotowane w trakcie leczenia mogą wskazywać na potencjalne dodatkowe działanie nefroprotekcyjne, poprzez utrzymanie wypełnienia żylnego łożyska naczyniowego i nerkowego ciśnienia perfuzyjnego.

Przeprowadzona w kolejnym etapie badania szczegółowa analiza wybranych parametrów biochemicznych w celu identyfikacji grupy pacjentów którzy odniosą większą korzyść z terapii będącej przedmiotem rozprawy, określonych w badaniu jako „good diuretic responders" (GDR), wykazała istotnie statystycznie większą zdolność do rozcieńczania moczu w 12 i 24 godzinie terapii, przy braku różnic w stężeniu w wartościach uNa/uCreat. Zwracała również uwagę istotnie mniejsza dawkę sumaryczna diuretyku pętlowego zastosowana w celu osiągnięcia zakładanego efektu diuretycznego. Ponadto pacjenci z grupy „*good diuretic responders*" (GDR) charakteryzowali się istotnie niższym stężeniem kreatyniny, magnezu i azotu mocznika (BUN) a w ocenie klinicznej mniejszym nasileniem objawów przewodnienia takich jak wypełnienie żył szyjnych (JVP), obrzęki obwodowe czy zastój w krążeniu płucnym. Szczegółowej analizie poddano stężenia jonów sodowych i chlorkowych elektrolitów w próbkach moczu (*spot urine samples*) pobranych w określonych przedziałach czasowych terapii. Mimo iż nie stwierdzono istotnych statystycznie różnic w stężeniach elektrolitów w próbkach moczu to warto zwrócić uwagę na wyższe stężenie jonów sodowych w 6 i 12 godzinie terapii w grupie *„good diuretic responders"*, co koresponduje z faktem iż natriureza jest silnym czynnikiem determinującym odpowiedź diuretyczną. Zaobserwowano również tendencję do wyższych stężeń endoteliny w kolejnych punktach czasowych u pacjentów lepiej odpowiadających na zastosowane leczenie, co może przemawiać za wzmożoną aktywacją tego układu jako mechanizmu kompensacyjnego w odpowiedzi na wzmożoną produkcję moczu przez nerki.

W ostatnich latach uwaga wielu badaczy skupia się na poszukiwaniu związku między stężeniami wybranych parametrów biochemicznych, ich rolą w mechanizmach odpowiedzialnych za przewodnienie i odpowiedź diuretyczną, a także ich znaczeniem jako niezależnych czynników pozwalających identyfikować pacjentów wysokiego ryzyka w

przebiegu epizodów dekompensacji niewydolności serca[25-30]. Podjęto zatem próbę precyzyjnego określenia profilu klinicznego grupy pacjentów z ostrą niewydolnością serca u których można spodziewać się dobrej odpowiedzi diuretycznej bez wzrostu ryzyka pogorszenia filtracji kłębuszkowej w przebiegu współistniejącej przewlekłej choroby nerek. Ograniczona liczebność grupy badanej nie pozwoliła jednak na uzyskanie istotnych statystycznie różnic.

Podsumowując, wyniki pracy mają wartość poznawczą i kliniczną oraz mogą wskazywać na potencjalną możliwość zastosowania systemu RenalGuard® w leczeniu wyselekcjonowanej grupy pacjentów z ostrą dekompensacją niewydolności serca i objawami przewodnienia, w połączeniu ze standardowym leczeniem diuretykiem dożylnie, jako bezpiecznej i efektywnej techniki kontrolowanego odwadniania. Jednocześnie, wobec szeroko rozpowszechnionego obecnie stosowania technik nerkozastępczych w oddziałach intensywnej terapii kardiologicznej, uzyskane wyniki badań mogą stanowić podstawę do dalszych prac nad określeniem dokładnego profilu hemodynamicznego i biochemicznego populacji pacjentów charakteryzujących się optymalnym efektem po zastosowaniu tej formy terapii a w konsekwencji poprawą rokowania w stale rosnącej grupie pacjentów z niewydolnością serca.

STRESZCZENIE

Stale rosnąca populacja chorych z niewydolnością serca jest w obecnych czasach jednym z najważniejszych problemów w ogólnie pojętej opiece zdrowotnej. Wraz z wiekiem z wiekiem pacjentów wciąż rośnie częstość rehospitalizacji z powodu niewydolności serca a w konsekwencji rosną koszty opieki zdrowotnej. Podejmowane są zatem działania w kierunku poszukiwania nowych, skuteczniejszych a zarazem bezpiecznych metod leczenia. Jednym z najczęstszych problemów klinicznych z jakim przychodzi zmierzyć się w leczeniu chorych z ostrą dekompensacją niewydolności serca (ADHF) jest skuteczna i bezpieczna eliminacja objawów przewodnienia.

Celem niniejszej pracy była ocena, zastosowanego po raz pierwszy w grupie pacjentów z ostrą dekompensacją niewydolności serca, połączenia standardowej terapii opartej na diuretyku pętlowym (furosemid) i metody kontrolowanego odwadniana z zastosowaniem systemu RenalGuard®, u pacjentów z zaawansowaną niewydolnością serca i współistniejącą przewlekłą chorobą nerek, hospitalizowanych z powodu ostrej dekompensacji niewydolności serca. W kolejnym etapie badania podjęto również próba identyfikacji grupy pacjentów którzy odniosą istotnie większą korzyść z tej formy terapii, na podstawie retrospektywnej analizy potencjalnego związku pomiędzy odpowiedzią diuretyczną, profilem klinicznym pacjentów i stężeniami wybranych markerów biochemicznych.

W ramach rozprawy przeprowadzono dwa badania, których wyniki opublikowano w recenzowanych czasopismach międzynarodowych w formie dwóch manuskryptów.

Pierwsza praca pt.” Controlled decongestion by Reprieve therapy in acute heart failure: results of the TARGET-1 and TARGET-2 studies.” obejmuje przeprowadzoną w sposób nierandomizowany, prospektywną analizę terapii 19 pacjentów z przewlekłą chorobą nerek hospitalizowanych z powodu ostrej dekompensacji niewydolności serca (klasa NYHA III-IV, RR 125 ± 14 / 73 ± 16 mmHg, eGFR 58 ± 24) z utrzymującymi się objawami przewodnienia w której stwierdzono, że zastosowanie systemu RenalGuard®, w połączeniu ze standardową terapią opartą na diuretyku pętlowym dożylnie, daje możliwość skutecznego i bezpiecznego, kontrolowanego odwadniania pacjentów hospitalizowanych z powodu ADHF z objawami przewodnienia. Procedura była dobrze tolerowana, żaden z pacjentów nie miał infekcji ani innych powikłań związanych z procedurą, zarówno w czasie jej trwania jak i po fazie leczenia. Podczas całego okresu leczenia skurczowe ciśnienie krwi pozostawało stabilne (123 ± 24 mmHg na początku, 115 ± 24 mmHg po 6 godzinach, 119 ± 19 mmHg po 12 godzinach i 116

± 20 mmHg na końcu terapii Renal Guard®; p = 0,19). Wszyscy pacjenci odnotowali istotną poprawę objawów niewydolności serca. W 30-dniowej obserwacji nie odnotowano zgonów ani poważnych zdarzeń niepożądanych w badanej populacji.

Druga praca pt.: "Diuretic treatment using the RenalGuard® system in patients hospitalized due to acute decompensated heart failure and characterization of the profile of patients with good and poor response to treatment – preliminary study." jest retrospektywną, ukierunkowaną analizą porównawczą wybranych parametrów klinicznych i biochemicznych w celu szczegółowego określenia parametrów związanych z lepszą odpowiedzią diuretyczną i największą korzyścią kliniczną po zastosowanej terapii z zastosowaniem systemu RenalGuard®, w której stwierdzono istotnie niższe stężenie kreatyniny, magnezu i azotu mocznika (BUN) oraz istotnie statystycznie większą zdolność do rozcieńczania moczu w 12 i 24 godzinie terapii w grupie pacjentów *„good diuretic responders"*, którzy charakteryzowali się ponadto mniejszym nasileniem objawów przewodnienia oraz mniejszą sumaryczną dawką diuretyku pętlowego potrzebną do osiągnięcia zakładanego efektu diuretycznego.

Na podstawie wyników badań uzyskanych w toku rozprawy wysunięto następujące wnioski:

1. Zastosowanie standardowej terapii diuretykiem pętlowym w połączeniu z systemem RenalGuard® daje możliwość skutecznego i bezpiecznego odwadniania pacjentów z przewlekłą chorobą nerek, hospitalizowanych z powodu ostrej dekompensacji niewydolności serca i objawami przewodnienia.
2. Precyzyjna identyfikacja parametrów hemodynamicznych i biochemicznych w grupie pacjentów z ADHF którzy odniosą największą korzyść z tej nowej formy terapii, przy zachowanym profilu bezpieczeństwa, wymaga przeprowadzenia dalszych badań na większej populacji chorych.
3. Istnieje uzasadniona potrzeba poszukiwania nowych metod efektywnego odwadniania w leczeniu pacjentów hospitalizowanych z powodu AHDF i objawami przewodnienia w celu poprawy wciąż złego rokowania w tej grupie chorych.

ABSTRACT

The constantly growing population of patients with heart failure is currently one of the most important problems in the general healthcare system. As patients age, the frequency of rehospitalizations due to heart failure is constantly increasing, and as a consequence, healthcare costs are rising. Therefore, actions are being taken to find new, more effective and safe methods of treatment. One of the most common clinical problems encountered in the treatment of patients with acute decompensated heart failure (ADHF) is the effective and safe elimination of symptoms of overhydration. The aim of this study was to evaluate the combination of standard therapy based on a loop diuretic (furosemide) and the method of controlled dehydration using the RenalGuard® system, used for the first time in a group of patients with acute decompensated heart failure, in patients with advanced heart failure and concomitant chronic kidney disease, hospitalized due to acute decompensated heart failure. In the next stage of the study, an attempt was also made to identify a group of patients who would benefit significantly more from this form of therapy, based on a retrospective analysis of the potential relationship between the diuretic response, the clinical profile of patients and the concentrations of selected biochemical markers.

As part of the dissertation, two studies were conducted, the results of which were published in peer-reviewed international journals in the form of two manuscripts.

The first paper entitled "Controlled decongestion by Reprieve therapy in acute heart failure: results of the TARGET-1 and TARGET-2 studies." includes a non-randomized, prospective analysis of the therapy of 19 patients with chronic kidney disease hospitalized due to acute decompensated heart failure (NYHA class III-IV, RR 125 ± 14 / 73 ± 16 mmHg, eGFR 58 ± 24) with persistent symptoms of overhydration, in which it was found that the use of the RenalGuard® system, in combination with standard therapy based on an intravenous loop diuretic, provides an opportunity for effective and safe, controlled dehydration of patients hospitalized due to ADHF with symptoms of overhydration. The procedure was well tolerated, none of the patients had infections or other complications related to the procedure, both during its duration and after the treatment phase. Systolic blood pressure remained stable throughout the treatment period (123 ± 24 mmHg at baseline, 115 ± 24 mmHg after 6 hours, 119 ± 19 mmHg after 12 hours, and 116 ± 20 mmHg at the end of Renal Guard® therapy; p = 0.19). All

patients noted significant improvement in heart failure symptoms. No deaths or serious adverse events were reported in the study population at 30 days.

The second work entitled: “Diuretic treatment using the RenalGuard® system in patients hospitalized due to acute decompensated heart failure and characterization of the profile of patients with good and poor response to treatment – preliminary study.“ is a retrospective, focused comparative analysis of selected clinical and biochemical parameters in order to determine in detail the parameters associated with a better diuretic response and the greatest clinical benefit after the therapy using the RenalGuard® system, in which a significantly lower concentration of creatinine, magnesium and urea nitrogen (BUN) was found and a statistically significantly greater ability to dilute urine in the 12th and 24th hour of therapy in the group of patients “good diuretic responders”, who were also characterized by a lower intensity of overhydration symptoms and a lower total dose of loop diuretic needed to achieve the assumed diuretic effect.

Based on the results of the research obtained during the dissertation, the following conclusions were drawn:

1. The use of standard loop diuretic therapy in combination with the RenalGuard® system enables effective and safe dehydration of patients with chronic kidney disease, hospitalized due to acute decompensation of heart failure and symptoms of overhydration.

2. Precise identification of hemodynamic and biochemical parameters in the group of patients with ADHF who will benefit the most from this new form of therapy, while maintaining a safety profile, requires further studies on a larger population of patients.

3. There is a justified need to search for new methods of effective dehydration in the treatment of patients hospitalized due to AHDF and symptoms of overhydration in order to improve the poor prognosis in this group of patients.

BIBLIOGRAFIA

1. Lelonek M., Pawlak A., Nessler J. i wsp. „Raport - Niewydolność serca w Polsce 2014-2021.” Asocjacja Niewydolności Serca PTK, (2023) ISBN 978-83-968813-0-4
2. McDonagh T.A. i wsp. “2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure” European Heart Journal (2021), Volume 42, Issue 36, 3599–3726. https://doi.org/10.1093/eurheartj/ehab368
3. Metra M, Felker GM, Zacà V, Bugatti S, Lombardi C, Bettari L, Voors AA, Gheorghiade M, Dei Cas L. Acute heart failure: Multiple clinical profiles and mechanisms require tailored therapy. *Int J Cardiol* 2010;144:175–179.
4. Analiza problemu zdrowotnego niewydolności serca (2014-2021). Aplikacja internetowa [udostępniona przez Ministerstwo Zdrowia]. Dostęp: https://analizy.mz.gov.pl:9443/WAS/app_NS/
5. Shah M.R. i wsp.” Hemodynamic profiles of advanced heart failure: association with clinical characteristics and long-term outcome.” Journal of heart failure 2001, Volume 7(2); 105-113.
6. Jardim S.I. i wsp. “A 2018 overview of diuretic resistance in heart failure.” Rev Port Cardiol. 2019;37(11):935---945
7. Mentz R.J. i wsp. “Decongestion in acute heart failure” European Journal of Heart Failure (2014) 16, 471–482.
8. Mullens W. i wsp. “The use of diuretics in heart failure with congestion – a position statement from the heart failure association of the European Society of Cardiology” European Heart Journal (2019), Volume 21(2); 137-155
9. Filippatos G. i wsp. “Global differences in characteristics, precipitants, and initial management of patients presenting with acute heart failure” JAMA Cardiol. 2020;5(4):401-410
10. Cleland JGF et al. Practical Applications of Intravenous Diuretic Therapy in Decompensated Heart Failure The American Journal of Medicine 2006;119;12;26-36
11. Cox Z.L. i wsp. “Compensatory post-diuretic renal sodium reabsorption is not a dominant mechanism of diuretic resistance in acute heart failure” Eur Heart Journal 2021 Volume 42(43):4468-4477
12. Verdani V. i wsp. “Worsening Renal Function in Patients Hospitalized with Acute Heart Failure: Risk Factors and Prognostic Significances” International Journal of Nephrology Volume 2011, Article ID 785974, 5 pages doi:10.4061/2011/785974

13. Levi T.M. i wsp. “Furosemide is associated with acute kidney injury in critically ill patients” Braz J Med Biol Res, September 2012, Volume 45(9):827-833
14. OECD. Health at a Glance 2021: OECD Indicators. 2021
15. Chioncel O. i wsp. “Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry.” European Journal of Heart Failure, 2017 Volume 19(20):1242-1254.
16. Costanzo M.R. i wsp. “Early ultrafiltration in patients with decompensated heart failure and diuretic resistance. J Am Coll Cardiol 2005;46:2047–51.
17. Bart B.A., Boyle A, Bank AJ, et al. Ultrafiltration versus usual care for hospitalized patients with heart failure: the relief for acutely fluidoverloaded patients with decompensated congestive heart failure (RAPID-CHF) trial. J Am Coll Cardiol 2005;46:2043– 6.
18. Constanzo M.R. i wsp. “Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure.” J Am Coll Cardiol. 2007 Feb 13;49(6):675-83. Epub 2007 Jan 26.
19. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O’Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, Ofili EO, Stevenson LW, Semigran MJ, Felker GM, Chen HH, Hernandez AF, Anstrom KJ, McNulty SE, Velazquez EJ, Ibarra JC, Mascette AM, Braunwald E; Heart Failure Clinical Research Network: Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med 2012;367:2296–2304.
20. Koratala A. i wsp. "Extracorporeal ultrafiltration for acute heart failure: lost battle or lasting opportunity?” Blood Purif 2017;43:1-10.
21. Briguori C. i wsp. “Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II): RenalGuard System in high-risk patients for contrast-induced acute kidney injury.” Circulation. 2011 Sep 13;124(11):1260-9. doi: 10.1161/CIRCULATIONAHA.111.030759. Epub 2011 Aug 15.
22. Marenzi G. i wsp. “Prevention of contrast nephropathy by furosemide with matched hydration: the MYTHOS (Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention) trial.” JACC Cardiovasc Interv. 2012 Jan;5(1):90-7. doi: 10.1016/j.jcin.2011.08.017
23. Mattathil S, Ghumman S, Weinerman J, Prasad A. “Use of the RenalGuard system to prevent contrast-induced AKI: A meta-analysis.” *Journal of Interventional Cardiology* 2017;30:480–487.

24. Luckraz H. i wsp. „Reduction in acute kidney injury post cardiac surgery using balanced forced diuresis: a randomized, controlled trial.” European Journal of Cardio-Thoracic Surgery 59 (2021) 562–569 doi:10.1093/ejcts/ezaa395
25. Zandijk A.J.L i wsp. „Chloride in heart failure. The neglected electrolyte.” J Am Coll Cardiol HF 2021;9:904-915
26. Kataoka H. “Chloride in heart failure syndrome: its pathophysiologic role and therapeutic implication.” Cardiol Ther (2021);10:407-428
27. Biegus J. i wsp. “Renal profiling based on estimated glomerular filtration rate and spot urine sodium identifies high-risk acute heart failure patients.” Eur J Heart Failure 2021;23(5):729-739
28. Nawrocka-Millward S. i wsp. „The role of urine chloride in acute heart failure”. Scientific Reports 14, 14100 (2024). https://doi.org/10.1038/s41598-024-64747-5
29. Iwanek G. i wsp. “Spot urine sodium-to-creatinine ratio surpasses sodium in identifying poor diuretic response in acute heart failure.” ESC Heart Failure (2024) Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/ehf2.14883
30. Guzik M. i wsp. “Spot urine sodium as a marker of urine dilution and decongestive abilities in acute heart failure.” Scientific Reports (2024) 14:1494 DOI:10.1038/s41598-024-51744-x

ZAŁĄCZNIKI

ZGODA KOMISJI BIOETYCZNEJ

Opinia Komisji Bioetycznej przy Uniwersytecie Medycznym we Wrocławiu (opinia nr KB – 210/2019)

OŚWIADZCENIA O WSPÓŁAUTORSTWIE

DOROBEK NAUKOWY

Paweł Siwołowski

1. Publikacje w czasopismach naukowych

1.1 Publikacje w czasopiśmie z IF

Lp	Opis bibliograficzny	IF	Punkty
1	Biegus Jan, Zymliński Robert, Szachniewicz Joanna, **Siwołowski Paweł**, Pawluś Aleksander, Banasiak Waldemar, Jankowska Ewa A., Ponikowski Piotr: Clinical characteristics and predictors of in-hospital mortality in 270 consecutive patients hospitalised due to acute heart failure in a single cardiology centre during one year, Kardiologia Polska, 2011, vol. 69, nr 10, s. 997-1005	0,515	13
2	Biegus Jan, Zymliński Robert, Sokolski Mateusz, Nawrocka Sylwia, **Siwołowski Paweł**, Szachniewicz Joanna, Jankowska Ewa A., Banasiak Waldemar, Ponikowski Piotr: Liver function tests in patients with acute heart failure, Polskie Archiwum Medycyny Wewnętrznej, 2012, vol. 122, nr 10, s. 471-479	1,833	10
3	Jankowska Ewa A., Kasztura Monika, Sokolski Mateusz, Bronisz Marek, Nawrocka Sylwia, Oleśkowska-Florek Weronika, Zymliński Robert, Biegus Jan, **Siwołowski Paweł**, Banasiak Waldemar, Anker Stefan D., Filippatos Gerasimos, Cleland John G.F., Ponikowski Piotr: Iron deficiency defined as depleted iron stores accompanied by unmet cellular iron requirements identifies patients at the highest risk of death after an episode of acute heart failure, European Heart Journal, 2014, vol. 35, nr 36, s. 2468-2476, DOI:10.1093/eurheartj/ehu235	15,203	50
4	Biegus Jan, Zymliński Robert, Sokolski Mateusz, **Siwołowski Paweł**, Gajewski Piotr, Nawrocka-Millward Sylwia, Poniewierka Elżbieta, Jankowska Ewa A., Banasiak Waldemar, Ponikowski Piotr: Impaired hepato-renal function defined by the MELD XI score as prognosticator in acute heart failure, European Journal of Heart Failure, 2016, vol. 18, nr 12, s. 1518-1521, DOI:10.1002/ejhf.644	6,968	40
5	Sokolski Mateusz, Zymliński Robert, Biegus Jan, **Siwołowski Paweł**, Nawrocka-Millward Sylwia, Todd John, Yerramilli Malli Rama, Estis Joel, Jankowska Ewa Anita, Banasiak Waldemar, Ponikowski Piotr: Urinary levels of novel kidney biomarkers and risk of true worsening renal function and mortality in patients with acute heart failure, European Journal of Heart Failure, 2017, vol. 19, nr 6, s. 760-767, DOI:10.1002/ejhf.746	10,683	40
6	Zymliński Robert, Sokolski Mateusz, **Siwołowski Paweł**, Biegus Jan, Nawrocka S., Jankowska Ewa A., Todd J., Yerramilli R., Estis J., Banasiak W., Ponikowski Piotr: Elevated troponin I level assessed by a new high-sensitive assay and the risk of poor outcomes in patients with acute heart failure, International Journal of Cardiology, 2017, vol. 230, s. 646-652, DOI:10.1016/j.ijcard.2017.01.012	4,034	40
7	Zymliński Robert, Biegus Jan, Sokolski Mateusz, **Siwołowski Paweł**, Nawrocka-Millward Sylwia, Todd John, Jankowska Ewa A., Banasiak Waldemar, Cotter Gad, Cleland John G., Ponikowski Piotr: Increased blood lactate is prevalent and identifies poor prognosis in patients with acute heart failure without overt peripheral hypoperfusion, European Journal of Heart Failure, 2018, vol. 20, nr 6, s. 1011-1018, DOI:10.1002/ejhf.1156	12,129	40

8	Sokolska Justyna Maria, Sokolski Mateusz, Zymliński Robert, Biegus Jan, **Siwołowski Paweł**, Nawrocka-Millward Sylwia, Jankowska Ewa Anita, Todd John, Banasiak Waldemar, Ponikowski Piotr: Patterns of dyspnoea onset in patients with acute heart failure: clinical and prognostic implications, ESC heart failure, 2019, vol. 6, nr 1, s. 16-26, DOI:10.1002/ehf2.12371	3,902	40
9	Zymliński Robert, Sokolski Mateusz, Biegus Jan, **Siwołowski Paweł**, Nawrocka-Millward Sylwia, Sokolska Justyna M., Dudkowiak Marta, Marciniak Dominik, Todd John, Jankowska Ewa A., Banasiak Waldemar, Ponikowski Piotr: Multi-organ dysfunction/injury on admission identifies acute heart failure patients at high risk of poor outcome, European Journal of Heart Failure, 2019, vol. 21, nr 6, s. 744-750, DOI:10.1002/ejhf.1378	11,627	200
10	Biegus Jan, Zymliński Robert, **Siwołowski Paweł**, Testani Jeffrey, Szachniewicz Joanna, Tycińska Agnieszka, Banasiak Waldemar, Halpert Andrew, Levin Howard, Ponikowski Piotr: Controlled decongestion by Reprieve therapy in acute heart failure: results of the TARGET-1 and TARGET-2 studies, European Journal of Heart Failure, 2019, vol. 21, nr 9, s. 1079-1087, DOI:10.1002/ejhf.1533	11,627	200
11	Biegus Jan, Zymliński Robert, Gajewski Piotr, Sokolski Mateusz, **Siwołowski Paweł**, Sokolska Justyna, Swoboda Katarzyna, Banasiak Maciej, Banasiak Waldemar, Ponikowski Piotr: Persistent hyperlactataemia is related to high rates of in-hospital adverse events and poor outcome in acute heart failure, Kardiologia Polska, 2019, vol. 77, nr 3, s. 355-362, DOI:10.5603/KP.a2019.0030	1,874	100
12	Zymliński Robert, Sierpiński Radosław, Metra Marco, Cotter Gad, Sokolski Mateusz, **Siwołowski Paweł**, Garus Mateusz, Gajewski Piotr, Tryba Joanna, Samorek Maria, Jankowska Ewa A., Biegus Jan, Ponikowski Piotr: Elevated plasma endothelin-1 is related to low natriuresis, clinical signs of congestion, and poor outcome in acute heart failure, ESC heart failure, 2020, vol. 7, nr 6, s. 3536-3544, DOI:10.1002/ehf2.13064	4,411	40
13	Sokolska Justyna Maria, Sokolski Mateusz, Zymliński Robert, Biegus Jan, **Siwołowski Paweł**, Nawrocka-Millward Sylwia, Swoboda Katarzyna, Gajewski Piotr, Jankowska Ewa Anita, Banasiak Waldemar, Ponikowski Piotr: Distinct clinical phenotypes of congestion in acute heart failure: characteristics, treatment response, and outcomes, ESC heart failure, 2020, vol. 7, nr 6, s. 3830-3840, DOI:10.1002/ehf2.12973	4,411	40
14	Krzesiński Paweł, Siebert Janusz, Jankowska Ewa Anita, Galas Agata, Piotrowicz Katarzyna, Stańczyk Adam, **Siwołowski Paweł**, Gutknecht Piotr, Chrom Paweł, Murawski Piotr, Walczak Andrzej, Szalewska Dominika, Banasiak Waldemar, Ponikowski Piotr, Gielerak Grzegorz: Nurse-led ambulatory care supported by non-invasive haemodynamic assessment after acute heart failure decompensation, ESC heart failure, 2021, vol. 8, nr 2, s. 1018-1026, DOI:10.1002/ehf2.13207	3,612	40
15	Krzesiński Paweł, Siebert Janusz, Jankowska Ewa Anita, Banasiak Waldemar, Piotrowicz Katarzyna, Stańczyk Adam, Galas Agata, Walczak Andrzej, Murawski Piotr, Chrom Paweł, Gutknecht Piotr, **Siwołowski Paweł**, Ponikowski Piotr, Gielerak Grzegorz: Rationale and design of the AMULET study: a new Model of telemedical care in patients with heart failure, ESC heart failure, 2021, vol. 8, nr 4, s. 2569-2579, DOI:10.1002/ehf2.13330	3,612	40

16	Krzesiński Paweł, Galas Agata, Piotrowicz Katarzyna, Stańczyk Adam, Siebert Janusz, Jankowska Ewa Anita, **Siwołowski Paweł**, Gutknecht Piotr, Chrom Paweł, Szalewska Dominika, Banasiak Waldemar, Ponikowski Piotr, Gielerak Grzegorz: The short-term benefit from nurseled ambulatory care supported by non-invasive haemodynamic assessment in patients after acute heart failure decompensation depends on time since hospital discharge, Kardiologia Polska, 2021, vol. 79, nr 78, s. 855-857, DOI:10.33963/KP.a2021.0012	3,71	100
17	Krzesiński Paweł, Jankowska Ewa A., Siebert Janusz, Galas Agata, Piotrowicz Katarzyna, Stańczyk Adam, **Siwołowski Paweł**, Gutknecht Piotr, Chrom Paweł, Murawski Piotr, Walczak Andrzej, Szalewska Dominika, Banasiak Waldemar, Ponikowski Piotr, Gielerak Grzegorz: Effects of an outpatient intervention comprising nurse-led non-invasive assessments, telemedicine support and remote cardiologists' decisions in patients with heart failure (AMULET study): a randomised controlled trial, European Journal of Heart Failure, 2022, vol. 24, nr 3, s. 565-577, DOI:10.1002/ejhf.2358	18,2	200
	Podsumowanie	118,351	1233

1.2 Publikacje w czasopiśmie bez IF

Lp	Opis bibliograficzny	Punkty
1	**Siwołowski Paweł**, Kübler Piotr, Banasiak Waldemar, Ponikowski Piotr: Blokery receptora angiotensyny AT1 - miejsce w leczeniu niewydolności serca, Choroby Serca i Naczyń, 2007, vol. 4, nr supl., A1-A7	3
2	Siennicka Agnieszka, Biegus Jan, Gajewski Piotr, Młynarska Katarzyna, Sokolski Mateusz, **Siwołowski Paweł**, Zymliński Robert, Jedynak Kamila, Ponikowska Beata, Urban Szymon: A pilot study on standardized in-hospital education about heart failure conducted during the first days after decompensation, Critical Pathways in Cardiology, 2023, vol. 22, nr 1, s. 13-18, DOI:10.1097/hpc.0000000000000313	40
	Podsumowanie	43

2. Monografie naukowe

2.1 Książka autorska - 2.2 Książka redagowana -

2.3 Rozdziały

Lp	Opis bibliograficzny	Punkty
1	Zymliński Robert, **Siwołowski Paweł**, Biegus Jan, Banasiak Waldemar, Ponikowski Piotr: Ostra niewydolność serca, W: Kardiologia : podręcznik oparty na zasadach EBM. T.2, (red.) Andrzej Szczeklik, Michał Tendera, Kraków 2010, Medycyna Praktyczna, s. 723-737, ISBN 978-83-7430-252-4	3
2	Ponikowski Piotr, Zymliński Robert, Biegus Jan, **Siwołowski Paweł**: Ostra niewydolność serca, W: Kardiologia : podręcznik Polskiego Towarzystwa Kardiologicznego, (red.) Piotr Ponikowski [i in.], Gdańsk 2019, Via Medica, s. 237245, ISBN 978-83-66311-40-4	20
3.	Paweł Krzesiński, **Paweł Siwołowski**, Waldemar Banasiak: Koncepcja AMULET a Program Kompleksowej Opieki nad Osobami z Niewydolnością Serca (KONS), W: Teleopieka ambulatoryjna w niewydolności serca, (red. nauk.) Paweł Krzesiński, Grzegorz Gielerak, Warszawa : PZWL, 2021, s.137-140, ISBN 978-83-948477-9-1	20
	Podsumowanie	43

3. Abstrakty

Lp	Opis bibliograficzny
1	Reczuch Krzysztof, Kübler Piotr, Jankowska Ewa, Wojtczak Marcin, **Siwołowski Paweł**, Skiba Jacek, Banasiak Waldemar, Ponikowski Piotr: Percutaneous coronary intervention in comparison with bypass surgery for left main coronary artery disease: 3 month follow-up of elective procedures, Kardiologia Polska, 2006, vol. 64, nr 8 supl.5, S327-S328 poz.P241, [X Jubileuszowy Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. GdyniaSopot-Gdańsk, 21-23 września 2006. Książka streszczeń]
2	Reczuch Krzysztof, Kübler Piotr, Jankowska Ewa, Wojtczak Marcin, **Siwołowski Paweł**, Skiba Jacek, Banasiak Waldemar, Ponikowski Piotr: Percutaneous coronary intervention in comparison with bypass surgery for left main coronary artery disease: 3-month follow-up of elective procedures, Kardiologia Polska, 2008, vol. 66, nr 9 supl.2, S108 poz.R096, [XII Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Poznań, 25-27 września 2008. Książka streszczeń]
3	**Siwołowski Paweł**, Jankowska Ewa A., Zymliński Robert, Biegus Jan, Bańkowski Tomasz, Banasiak Waldemar, Ponikowski Piotr: Ocena efektów leczenia chorych z dekompensacją skrajnie ciężkiej przewlekłej niewydolności serca za pomocą ultrafiltracji żylno-żylnej - raport wstępny, Kardiologia Polska, 2010, vol. 68, nr supl.3, S156 poz.R071, [XIV Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Poznań, 23-25 września 2010 r. Książka streszczeń]
4	Biegus Jan, Zymliński Robert, Szachniewicz J., **Siwołowski Paweł**, Nawrocka S., Banasiak W., Jankowska Ewa A., Ponikowski Piotr: Predictors of 30- and 180-day mortality in 326 consecutive patients admitted due to acute heart failure in one cardiology centre, European Journal of Heart Failure Supplements, 2011, vol. 10, nr suppl.1, S11 poz.P200, [Heart Failure Congress 2011. Gothenburg (Sweden), 21-24 May 2011]
5	Sokolski Mateusz, Biegus Jan, Zymliński Robert, **Siwołowski Paweł**, Nawrocka S., Banasiak W., Jankowska Ewa A., Ponikowski Piotr: Changes in laboratory and clinical parameters during 48h of hospitalization as predictors of 30- and 180-day mortality in 326 consecutive patients admitted due to acute heart failure, European Journal of Heart Failure Supplements, 2011, vol. 10, nr suppl.1, S61 poz.P396, [Heart Failure Congress 2011. Gothenburg (Sweden), 21-24 May 2011]
6	Biegus Jan, Sokolski Mateusz, Zymliński Robert, Kulej Katarzyna, Szachniewicz Joanna, **Siwołowski Paweł**, Nawrocka Sylwia, Banasiak Waldemar, Jankowska Ewa A., Ponikowski Piotr: Czynniki determinujące śmiertelność 30- i 180-dniową u 326 kolejnych pacjentów hospitalizowanych z powodu ostrej niewydolności serca w jednym ośrodku kardiologicznym, W: XV Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Wrocław, 6-8. 10. 2011 r. Abstrakty [CD-ROM] 2011, poz.031
7	Sokolski Mateusz, Biegus Jan, Zymliński Robert, Szachniewicz Jolanta, **Siwołowski Paweł**, Nawrocka Sylwia, Pawluś Aleksander, Banasiak Waldemar, Jankowska Ewa A., Ponikowski Piotr: Zmiany parametrów laboratoryjnych oraz parametrów klinicznych w ciągu pierwszych 48 h hospitalizacji, jako predyktory zgonu w obserwacji 30- oraz 180-dniowej u 326 kolejnych [chorych przyjętych z powodu ostrej niewydolności serca], W: XV Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Wrocław, 6-8. 10. 2011 r. Abstrakty [CD-ROM] 2011, poz.P030
8	Biegus Jan, Zymliński Robert, Sokolski Mateusz, Nawrocka Sylwia, **Siwołowski Paweł**, Szachniewicz Joanna, Jankowska Ewa Anita, Banasiak Waldemar, Ponikowski Piotr: Kliniczne znaczenie zmiany stężenia hemoglobiny w czasie pierwszych 48 godzin leczenia u pacjentów z ostrą niewydolnością serca, Kardiologia Polska, 2012, vol. 70, nr supl.3, poz.P058, [XVI Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Poznań, 20-22 września 2012. Streszczenia]

9	Biegus Jan, Zymliński Robert, Sokolski Mateusz, Nawrocka Sylwia, **Siwołowski Paweł**, Szachniewicz Joanna, Jankowska Ewa Anita, Banasiak Waldemar, Ponikowski Piotr: Częstość występowania i wpływ na rokowanie dysfunkcji wątroby u pacjentów z ostrą niewydolnością serca, Kardiologia Polska, 2012, vol. 70, nr supl.3, poz.P065, [XVI Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Poznań, 20-22 września 2012. Streszczenia]
10	Sokolski Mateusz, Zymliński Robert, Nawrocka Sylwia, Biegus Jan, **Siwołowski Paweł**, Szachniewicz Joanna, Josiak Krystian, Banasiak Waldemar, Jankowska Ewa Anita, Ponikowski Piotr: Zastosowanie wziewnego iloprostu w teście reaktywności łożyska płucnego u chorych z wtórnym nadciśnieniem płucnym z wadą zastawkową serca i/lub lewokomorową niewydolnością serca, Kardiologia Polska, 2012, vol. 70, nr supl.3, poz.U089, [XVI Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Poznań, 20-22 września 2012. Streszczenia]
11	Zymliński Robert, Biegus Jan, Sokolski Mateusz, Nawrocka S., **Siwołowski Paweł**, Szachniewicz J., Cotter G., Jankowska Ewa A., Banasiak W., Ponikowski Piotr: Elevated serum lactate is a marker of organ damage related to impaired hemodynamics and indicates poor prognosis in acute heart failure, European Heart Journal, 2013, vol. 34, 294 poz.P1517, [European Society of Cardiology Congress 2013. Amsterdam (Netherlands), 31 August - 4 September 2013]
12	Zymliński Robert, Biegus Jan, Sokolski Mateusz, Nawrocka N., **Siwołowski Paweł**, Szachniewicz J., Cotter G., Jankowska Ewa A., Banasiak W., Ponikowski Piotr: Elevated serum lactate is a marker of organ hypoperfusion and indicates poor prognosis in acute heart failure, European Journal of Heart Failure Supplements, 2013, vol. 12, nr suppl.1, S153 poz.P1419, [Heart Failure Congress 2013. Lisbon (Portugal), 25-28 May 2013]
13	Biegus Jan, Zymliński Robert, Sokolski Mateusz, Nawrocka S., **Siwołowski Paweł**, Szachniewicz J., Jankowska Ewa A., Cotter G., Banasiak W., Ponikowski Piotr: Impaired hemodynamics and liver dysfunction in acute heart failure, European Journal of Heart Failure Supplements, 2013, vol. 12, nr suppl.1, S193 poz.P1405, [Heart Failure Congress 2013. Lisbon (Portugal), 25-28 May 2013]
14	Sokolski Mateusz, Zymliński Robert, Biegus Jan, **Siwołowski Paweł**, Nawrocka S., Szachniewicz J., Banasiak W., Jankowska Ewa A., Ponikowski Piotr: Validation of impedance cardiography with invasive measurements of haemodynamic parameters in patients with advanced heart failure, European Journal of Heart Failure Supplements, 2013, vol. 12, nr suppl.1, S322 poz.P995, [Heart Failure Congress 2013. Lisbon (Portugal), 25-28 May 2013]
15	Biegus Jan, Zymliński Robert, Sokolski Mateusz, Nawrocka Sylwia, **Siwołowski Paweł**, Szachniewicz Joanna, Banasiak Waldemar, Jankowska Ewa, Ponikowski Piotr: Zaburzenia hemodynamiczne a funkcja wątroby u pacjentów z ostrą i przewlekłą niewydolnością serca, Kardiologia Polska, 2014, vol. 72, nr supl.3, s. 249-250, [XVIII Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Poznań, 18-20 września 2014. Streszczenia]
16	Zymliński Robert, Sokolski Mateusz, Biegus Jan, **Siwołowski Paweł**, Jankowska Ewa A., Todd J., Yerramilli R., Estis J., Banasiak W., Ponikowski Piotr: Increase in ultra-sensitive troponin I is associated with poor prognosis in patients with acute heart failure, European Heart Journal, 2015, vol. 36, 1179 poz.P6569, [European Society of Cardiology Congress 2015. London (UK), 29 August - 2 September 2015]
17	Sokolski Mateusz, Zymliński Robert, Biegus Jan, **Siwołowski Paweł**, Jankowska Ewa A., Todd J., Yerramilli R., Estis J., Banasiak W., Ponikowski Piotr: Determinants of plasma kidney injury molecule-1 and its prognostic utility in patients with acute heart failure, European Heart Journal, 2015, vol. 36, 156 poz.P889, [European Society of Cardiology Congress 2015. London (UK), 29 August - 2 September 2015]
18	Biegus Jan, Zymliński Robert, **Siwołowski Paweł**, Sokolski Mateusz, Jankowska Ewa A., Banasiak W., Ponikowski Piotr: Hepato-renal dysfunction on admission predicts the outcome in acute heart failure, European Heart Journal, 2015, vol. 36, 547 poz.3308, [European Society of Cardiology Congress 2015. London (UK), 29 August - 2 September 2015]

19	Sokolski Mateusz, Zymliński Robert, Biegus Jan, **Siwołowski Paweł**, Jankowska Ewa, Todd John, Yerramilli Rama, Estis Joel, Banasiak Waldemar, Ponikowski Piotr: Determinants of plasma kidney injury molecule-1 and its prognostic utility in patients with acute heart failure, Kardiologia Polska, 2015, vol. 73, nr supl.4, s. 273-274, [XIX Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Wrocław, 1-3 października 2015. Streszczenia]
20	Sokolski Mateusz, Zymliński Robert, Biegus Jan, **Siwołowski Paweł**, Jankowska Ewa, Todd John, Yerramilli Rama, Estis Joel, Banasiak Waldemar, Ponikowski Piotr: Novel urinary kidney biomarkers predict worsening renal function in patients with acute heart failure, Kardiologia Polska, 2015, vol. 73, nr supl.4, s. 316-317, [XIX Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Wrocław, 1-3 października 2015. Streszczenia]
21	Sokolski Mateusz, Zymliński Robert, Biegus Jan, **Siwołowski Paweł**, Nawrocka S., Krzysztofik Justyna, Todd J., Estis J., Jankowska Ewa A., Banasiak W., Ponikowski Piotr: Increased levels of urinary biomarkers of tubular injury as a predictor of poor diuretic respons e in acute heart failure, European Heart Journal, 2016, vol. 37, 221 poz.P1175, [European Society of Cardiology Congress 2016. Rome (Italy), 27-31 August 2016]
22	Zymliński Robert, Sokolski Mateusz, Biegus Jan, **Siwołowski Paweł**, Nawrocka S., Krzysztofik Justyna, Jankowska Ewa A., Banasiak W., Ponikowski Piotr: Prognostic significance of multi-organ dysfunction/damage in acute heart failure, European Journal of Heart Failure, 2016, vol. 18, nr suppl.1, 22 poz.129, [Heart Failure 2016 Conference. Florence (Italy), 21-24 May 2016. Abstracts]
23	Zymliński Robert, Sokolski Mateusz, Biegus Jan, **Siwołowski Paweł**, Todd J., Estis J., Florey S., Jankowska Ewa A., Banasiak W., Ponikowski Piotr: Serial troponin assessment in the early phase of hospitalization for acute heart failure to identify high risk patients, European Journal of Heart Failure, 2016, vol. 18, nr suppl.1, 246-247 poz.P1051, [Heart Failure 2016 Conference. Florence (Italy), 21-24 May 2016. Abstracts]
24	Sokolski Mateusz, Zymliński Robert, Biegus Jan, **Siwołowski Paweł**, Todd J., Yerramilli R., Estis J., Jankowska Ewa A., Banasiak W., Ponikowski Piotr: Urinary levels of new kidney biomarkers and risk of worsening renal function and mortality in patients with acute heart failure, European Journal of Heart Failure, 2016, vol. 18, nr suppl.1, 366 poz.P1573, [Heart Failure 2016 Conference. Florence (Italy), 21-24 May 2016. Abstracts]
25	Zymliński Robert, Sokolski Mateusz, Biegus Jan, Nawrocka Sylwia, **Siwołowski Paweł**, Todd John, Estis Joel, Florey Sarah, Jankowska Ewa, Banasiak Waldemar, Ponikowski Piotr: Highsensitive cardiac troponin I in diagnosis of early myocardial damage in patients with acute heart failure, Kardiologia Polska, 2016, vol. 74, nr supl.4, s. 221-222, [XX Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Poznań, 15-17 września 2016 r. Streszczenia]
26	Sokolski Mateusz, Zymliński Robert, Biegus Jan, **Siwołowski Paweł**, Krzysztofik Justyna, Todd John, Estis Joel, Jankowska Ewa, Banasiak Waldemar, Ponikowski Piotr: Increased levels of urinary biomarkers of tubular injury as a predictor of poor diuretic response in acute heart failure, Kardiologia Polska, 2016, vol. 74, nr supl.4, s. 231-232, [XX Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Poznań, 15-17 września 2016 r. Streszczenia]
27	Zymliński Robert, Sokolski Mateusz, Biegus Jan, **Siwołowski Paweł**, Nawrocka Sylwia, Jankowska Ewa, Banasiak Waldemar, Ponikowski Piotr: Prognostic significance of multiorgan dysfunction/damage in acute heart failure, Kardiologia Polska, 2016, vol. 74, nr supl.4, s. 355-356, [XX Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Poznań, 15-17 września 2016 r. Streszczenia]
28	Sokolski Mateusz, Zymliński Robert, Biegus Jan, **Siwołowski Paweł**, Nawrocka-Millward S., Krzysztofik Justyna, Jankowska Ewa A., Banasiak W., Ponikowski Piotr: Determinants of true worsening renal function and its prognostic meaning in patients with acute heart failure, European Heart Journal, 2017, vol. 38, nr suppl.1, 20 poz.139, [European Society of Cardiology Congress 2017. Barcelona (Spain), 26-30 August, 2017]

29	Sokolski Mateusz, Zymliński Robert, Biegus Jan, **Siwołowski Paweł**, Nawrocka-Millward S., Krzysztofik Justyna M., Jankowska Ewa A., Banasiak W., Ponikowski Piotr: True worsening renal function identifies patients with acute heart failure with an ominous outcome, European Journal of Heart Failure, 2017, vol. 19, nr suppl.1, 199-200 poz.885, [Heart Failure 2017 and the 4th World Congress on Acute Heart Failure. Paris, France, 29 April - 2 May 2017. Abstracts]
30	Krzysztofik Justyna M., Sokolski Mateusz, Zymliński Robert, Biegus Jan, **Siwołowski Paweł**, Nawrocka-Millward S., Banasiak W., Jankowska Ewa A., Ponikowski Piotr: Patterns of dyspnoea onset, clinical characteristics and the outcomes in patients with acute heart failureimplications for clinical trials, European Journal of Heart Failure, 2017, vol. 19, nr suppl.1, 548 poz.P2145, [Heart Failure 2017 and the 4th World Congress on Acute Heart Failure. Paris, France, 29 April - 2 May 2017. Abstracts]
31	Sokolski Mateusz, Zymliński Robert, Biegus Jan, **Siwołowski Paweł**, Nawrocka-Millward Sylwia, Krzysztofik Justyna, Jankowska Ewa, Banasiak Waldemar, Ponikowski Piotr: "True" worsening renal function identifies patients with acute heart failure with an ominous outcome, Kardiologia Polska, 2017, vol. 75, nr supl.4, s. 22-23, [XXI Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Katowice, 21-23 września 2017. Streszczenia. Toż s.141-142]
32	Krzysztofik Justyna, Sokolski Mateusz, Zymliński Robert, Biegus Jan, **Siwołowski Paweł**, Nawrocka Sylwia, Banasiak Waldemar, Jankowska Ewa, Ponikowski Piotr: Association between orthopnea onset, clinical characteristics and outcomes in patients with acute heart failure - implication for clinical trials, Kardiologia Polska, 2017, vol. 75, nr supl.4, s. 363-364, [XXI Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego. Katowice, 21-23 września 2017. Streszczenia]
33	Krzysztofik Justyna M., Sokolski Mateusz, Zymliński Robert, Biegus Jan, **Siwołowski Paweł**, Nawrocka-Millward S., Banasiak W., Jankowska Ewa A., Ponikowski Piotr: Patterns of dyspnoea onset in patients with acute heart failure - clinical and prognostic implications, European Heart Journal: Acute Cardiovascular Care, 2018, vol. 7, nr suppl.1, 67-68 poz.P156, [Acute Cardiovascular Care Congress 2018. Milan (Italy), 3-5 March 2018. Abstracts]
34	Sokolski Mateusz, Sokolska Justyna M., Zymliński Robert, Biegus Jan, Swoboda K., **Siwołowski Paweł**, Gajewski Piotr, Nawrocka-Millward S., Banasiak W., Ponikowski Piotr: The significance of plasma osmolarity for in-hospital course and long-term outcome in patients with acute heart failure, European Journal of Heart Failure, 2019, vol. 21, nr suppl.1, 106-107 poz.P454, [Heart Failure 2019 and the World Congress on Acute Heart Failure. Athens, Greece, 25-28 May 2019. Abstracts]
35	Sokolska Justyna M., Sokolski Mateusz, Zymliński Robert, Biegus Jan, Swoboda K., **Siwołowski Paweł**, Nawrocka-Millward S., Gajewski Piotr, Banasiak W., Ponikowski Piotr: Acute heart failure has many faces - clinical characteristics, response to the treatment and long-term outcome in patients with different physical presentations of cardiac decompensation, European Journal of Heart Failure, 2019, vol. 21, nr suppl.1, 539-540 poz.P2090, [Heart Failure 2019 and the World Congress on Acute Heart Failure. Athens, Greece, 25-28 May 2019. Abstracts]
36	Krzesinski P, Galas A, Piotrowicz K, Chrom P, Jankowska Ewa Anita, Siebert J, Stanczyk A, **Siwołowski Paweł** Marcin, Gutknecht P, Szalewska D, Banasiak W, Ponikowski Piotr, Gielerak G: The beneficial effects of adherence to outpatient telecare intervention on clinical outcomes after an episode of acute heart failure: insights from the prospective randomised controlled AMULET trial, European Heart Journal, 2023, vol. 44, nr suppl.2, poz.ehad655.2976, [ESC Congress 2023. Amsterdam, Netherlands, 25-28 August 2023]

Impact factor: 118,351

Punkty ministerialne: 1319,0

OSOBA SPORZĄDZAJĄCA: PIOTR ORNAWKA

DZIAŁ BIBLIOGRAFII I BIBLIOMETRII BG UMW