Clinical evaluation of the Transcatheter Renal Venous Decongestion (TRVD) System for renal venous decongestion in patients with Acute Decompensated Heart Failure (ADHF)

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The objective of this study is to assess the feasibility and initial safety and performance of the TRVD* System when used for renal venous decongestions in patients with acute decompensated heart failure.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON46072

Source
ToetsingOnline

Brief title
TRVD II

Condition

- Heart failures
- Renal and urinary tract therapeutic procedures

Synonym
Acute Decompensated Heart Failure, Heart failure

Research involving
Human

Sponsors and support

Primary sponsor: Magenta Medical Ltd.
Source(s) of monetary or material Support: Company: Magenta Medical Ltd;Israel

Intervention

Keyword: Acute Decompensated Heart Failure, Clinical evaluation, Renal venous decongestion, Transcatheter system

Outcome measures

Primary outcome

- Safety -

Serious Adverse Events (SAE): device related SAEs rate through 30 days post index procedure (Refer to definition in Appendix B). Safety data will be collected throughout study period.

- Feasibility -

Technical Success: Successful delivery and deployment of the RVD* Catheter via the RVD* Introducer, on an intention-to-treat basis, adequate function during device operation and successful retrieval of the RVD* Catheter and RVD* Introducer.

Procedural Success: Technical Success and the absence of device-related SAE through hospital discharge.

Secondary outcome

- RVP reduction from baseline during therapy: assessed in hospital

- CVP reduction from baseline: assessed in hospital

- Total net fluid loss from baseline: assessed in hospital (post urine catheter placement till removal).

- In-hospital daily change in body weight.

- Change in parameters of sodium excretion (sodium/potassium ration, total and fractional excretion of sodium) from baseline to 24, 48, 72 and 96 hours and discharge.

- Change in IVC dimensions and collapsibility index per ultrasound from baseline to 24, 48 and 96 hours and discharge.

- Ultrasonic evidence of decongestion (as per IVC size) at 24, 48 and 96 hours and discharge.

- Change in neuroendocrine profile (plasma renin and aldosterone levels) throughout hospitalization and at 30-day follow up (not obligatory per protocol).

- In-hospital daily change and follow-up change in Patient Global Assessment (PGA) and dyspnea using the Visual Analogue Scale (VAS) compared to baseline.

- Change in the cardiac biomarker (NT-proBNP or BNP) from baseline to 24, 48, 72 and 96 hours and discharge.

- Change in renal biomarkers (urinary NGAL and KIM-1 and serum Cystatin C) from baseline to 48, 72 and 96 hours and discharge (not obligatory per protocol).

- Plasma free haemoglobin at baseline, 6, 12, 24, 48, 72, 96 hours and hospital discharge.

- Change in body weight at follow-up compared to baseline.

- Clinical decongestion at 48 and 96 hours, as well as hospital discharge, 30 days and 90 days following discharge. Clinical congestion will be graded based on edema, rales, jugular venous pressure, and weight.

*- Change in creatinine from baseline to discharge and at the 90-day follow-up visit; peak creatinine during hospitalization.

*- In-hospital daily change in serum electrolytes (sodium, potassium and chloride)

*- In-hospital daily change in IV diuretic dose.

*- Diuretic response defined as urinary Sodium content/loop diuretic dose as well as total urinary volume/loop diuretic dose (obligatory per protocol only as long as urine output is measured via a bladder catheter).

- Echocardiographic changes in cardiac function from baseline to discharge and 30-day.

- Worsening of heart failure: failure to improve (persistent signs and symptoms of HF until discharge despite therapy) or worsening signs and symptoms of HF despite therapy, requirement for 'rescue therapy' i.e., the need to initiate or intensify intravenous therapy (such as inotropes or intravenous vasoactive agents) or implement mechanical cardiac or ventilatory support. Worsening of heart failure will be assessed throughout hospitalization.

- Heart failure related re-hospitalization at 30, 60 and 90 days following discharge.

- Mortality during hospitalization and throughout follow-up period.

Study description

Background summary

Heart failure (HF) is a pandemic affecting over 26 million people worldwide, among them 6.5-9 million Europeans and more than 5.5 million Americans. Population-based studies have estimated that approximately 1-2% of adults in developed countries suffer from HF, with the prevalence rising to over 10% among persons 70 years of age or older. This population segment is projected to grow as the survival rates of both ischemic heart disease and HF are improving, while the general population is aging. Between 1.1 and 1.4 million new cases of HF are diagnosed annually in the European Union and the US combined. HF is also on the rise in the developing world due to significant increases in the prevalence of its
risk factors, such as hypertension, diabetes, and obesity (WHO report; World Health Statistics 2012: Non-communicable Diseases: A major health challenge of the 21st century).HF is characterized not only by high mortality (about 50% in 5 years, comparable to intermediate cancer mortality), but also by high morbidity: it is the number one cause for hospitalization of patients 65 years of age or older. Recurrent hospital admissions place a
heavy burden not only on patients and their families, but also on society, amounting to 60-80% of total HF costs, which are expected to double during the next 15 years (reaching a staggering $70 billion in the US alone).

Data from the EuroHeart Failure Survey, as well as the American Acute Decompensated Heart Failure National Registry (ADHERE), show that hospitalization for worsening HF is in 90% of the cases due to the signs and symptoms of congestion (e.g., jugular venous distension, rales, hepatomegaly, and peripheral oedema), rather than to low cardiac output. Although congestion is the main reason for hospitalization, patients are frequently discharged with persistent signs of congestion, which may very well contribute to the consistently high readmission rates observed in ADHF. Venous congestion can be quantified by physical examination, distension of the inferior vena cava on ultrasound or direct measurement of the elevated central venous pressure. The kidneys, which play a central role in the pathophysiology of HF, are particularly vulnerable to congestion. Since they are encapsulated and thus susceptible to compression, increased central venous pressure resulting from cardiac
dysfunction increases renal venous pressure, which is transmitted back to the renal parenchyma. The resulting renal congestion has been shown to decrease renal blood flow, glomerular filtration rate, and tubular sodium excretion; it leads to activation of the renin-angiotensin-aldosterone axis and the sympathetic nervous system, and cause hypo-responsiveness to natriuretic peptides and diuretics. These cardio-renal interactions lead to
fluid retention and to renal and systemic vasoconstriction, further aggravating the syndrome in a reinforcing feedback loop. As a result, renal dysfunction is present in about 40% of patients with HF, develops or worsens in about 30% of patients admitted with ADHF, and has a profound clinical impact: increasing the in-hospital death rate 7-fold, and the length of patients with HF, develops or worsens in about 30% of patients admitted with ADHF, and has a profound clinical impact: increasing the in-hospital death rate 7-fold, and the length

of stay 3-fold.

Importantly, worsening renal function and diuretic hypo-responsiveness in patients with ADHF are a dynamic, potentially interlinked phenomenon that develops immediately following hospitalization and up to 72 hours thereafter. Consequently, there is a need * and indeed a window of therapeutic opportunity * for early intervention to not only protect the kidneys during this vulnerable phase and prevent worsening renal function, but also enhance and improve renal function. Based on relevant state-of-the-art experimental data, such an intervention, although limited in duration (up to 24 hours), is expected to result in substantial health benefits weeks and months beyond the acute phase of hospitalization.

While efforts are underway to improve guideline adherence to recommended medical therapy, such efforts are unlikely to have a dramatic impact on outcomes and costs. In the Western world, use of beta-blocking agents, ACE-inhibitors, and angiotensin receptor blockers is widespread, as is the use of diuretics. Comorbidities in the elderly may limit the possibility of reaching target dosages recommended based on controlled randomized trials. More importantly, according to leading experts, the development of new and effective heart failure drugs is unlikely to occur in the foreseeable future, as this would first entail the discovery of hitherto unknown neurobiological and/or endocrine pathways. In acute and worsening heart failure, diuretics * a double-edged sword * remain the mainstay of therapy, with none of the newer pharmacological agents tested (inotropes, vasodilators, adenosine, vasopressin inhibitors) showing favorable impact on outcomes.

As for device therapy, currently, there are only two guideline-supported device therapies for the treatment of HF3: Cardiac Resynchronization Therapy (CRT) and Ultrafiltration (UF).

Cardiac Resynchronization Therapy is a chronic therapy that requires implantation of a pacemaker for biventricular stimulation and affects outcomes favorably, but only about 15% of patients fulfill the clinical and electrocardiographic eligibility criteria, and of those eligible, the response rate varies (about 50-60%). In any case, it is not an option for the treatment of patients just admitted for acute and worsening heart failure. Ultrafiltration, initially promising to overcome the drawbacks of diuretics, was shown to be inferior to standard diuretic therapy in preventing deterioration of renal function in hospital-admitted patients and did not increase the rate of adequate decongestion at 96 hours (which still stands at around 10% only).

The clinical dilemma surrounding decongestion may be summarized as follows: while sluggish fluid removal in ADHF may keep renal venous and interstitial pressures elevated for a protracted period of time, and thus promote ongoing kidney injury, too rapid fluid removal imposed on deteriorating kidneys may

result in further kidney injury through excessive intravascular volume depletion. We therefore propose to selectively reduce renal venous pressure in patients with ADHF, shortly after hospital admission, for a period of up to 24 hours , in order to mechanically unload the kidneys as early as possible, improve renal perfusion and function, and interrupt the activation of neuroendocrine vasoconstrictor
systems, thus promoting diuresis in a physiologic manner. Reduction in renal venous pressure is also expected to overcome diuretic resistance, avoid the need for escalating diuretic dosages, and potentially enable a reduction in diuretic dosages.

In summary, there is an urgent need as well as an important opportunity for a transcatheter heart failure therapy to reduce readmission rates, improve outcomes and reduce costs. This can be achieved by relieving kidney congestion - which results from heart failure, complicates it, and aggravates it - employing a safe, simple, and elegant transcatheter approach.

Expected benefits:
- Promote safe and effective decongestion in acute and worsening HF
- Preserve and restore renal function
- Overcome diuretic resistance
- Obviate the need for high-dose diuretics
- Simple venous access (avoid risks of arterial catheterization, allow use in regular ward)
- Reduce readmission rates
- Improve outcomes and thus reduce costs

According to this rationale, Magenta Medical is developing the TRVD* System - a transcatheter renal venous decongestion system for the treatment of Acute Decompensated Heart Failure (ADHF) by reducing elevated renal venous pressure in order to preserve and restore renal function, facilitate diuresis and sodium removal, and enhance decongestion. The proposed clinical study will assess the feasibility and initial safety and performance of this therapy.

Study objective

The objective of this study is to assess the feasibility and initial safety and performance of the TRVD* System when used for renal venous decongestions in patients with acute decompensated heart failure.

Study design

This is a prospective, multi-center, multi-national, non-randomized, open-label clinical study of the TRVD* System. The study will include patients who met all eligibility criteria and in whom RVD* Catheter deployment was attempted. The study will be conducted in up to 10 centers in Europe (Belgium and The

Netherlands) and Israel.

The duration of participation for each patient will be approximately 3 months. Patients hospitalized for ADHF will be screened and if meeting the study eligibility criteria will be treated with the TRVD* System for up to 24 hours. Patients will be evaluated from enrollment until hospital discharge, then at 30-, 60-, and 90-days post procedure.

Measures to minimize bias:
By nature of the type of the proposed study, blinding of the investigator is not feasible. However, several measures will be implemented to minimize systematic error/bias:
- Screening log will be completed by investigational sites listing all ADHF patients consented to the TRVD* II study. The log will include reasons for exclusion from the study.
- Measurements made by CT and US (for IVC measurements) will be standardized by use of a pre-specified protocol; measurements made by echocardiography will follow the site*s standard of care for full cardiac ultrasonography.
- Investigator*s reported device related serious adverse events will be reviewed and adjudicated. The adjudicated results will be used in all cases for purposes of data analysis. *
- Medical monitoring will take place in reviewing safety data and ensuring appropriate reporting of adverse events. The sponsor and principal investigator will oversee the overall safety of the study.
- Clinical monitor will verify patients* data and ensure compliance with good clinical practice (GCP), CIP and other study requirements.

Intervention

The TRVD* System is to be used during a renal venous catheterization procedure. In brief, a single procedure is performed by inserting the RVD* Steerable Introducer into the femoral vein and advancing it to the renal vein. The RVD* Catheter is then introduced into the RVD* Steerable Introducer; once fully in place, the pump head expands. The pressure at the tip of the catheter reflects the renal venous pressure (RVP) and the TRVD* Console will operate the propeller at the speed that is needed to equate the measured pressure to the set target pressure. Depending on the anatomy, a second RVD* Steerable Introducer and RVD* Catheter may be placed in the contralateral renal vein. The device may remain in the body for up to 24 hours from the insertion of the first Introducer through the femoral vein.
Following therapy, the System can be removed either bedside or under fluoroscopy. Concomitant with the TRVD* therapy, anticoagulation agents are given to inhibit thrombus formation and IV analgesic and sedative drugs are administered as needed, and in accordance with standard of care.
Diuretics should be given continuously at a constant intravenous dosage during baseline (after insertion of a urinary bladder catheter) and for at least 24 hours following initiation of TRVD therapy. Bolus administration on top of

continuous intravenous therapy should be avoided, unless clinically necessary. Specifics of the device use instructions, warning and contraindications are provided in the Instructions for Use manual.

Study burden and risks

The primary risks of the procedure are similar to the risks of all procedures requiring venous catheterization. The following are possible risks of the catheterization procedure, which includes the TRVD* procedure (arranged alphabetically):
- Allergic and/or adverse reaction from insertion of foreign body (i.e., catheter)
- Cardiopulmonary arrest
- Complications associated with the contrast agent that might be used during the procedure, e.g., serious allergic reaction or reduced kidney function
- Complications associated with the use of any medication during or after the procedure
- Complications at catheter insertion site in the groin:
- AV fistula
- Bruising
- Haematoma
- Infection
- Pain
- Significant bleeding
- Death
- Electrolyte disturbances
- Embolism, including thromboembolism which might cause temporary or permanent damage to end organs. Thromboembolism might result in pulmonary embolism, kidney damage, or peripheral ischemia.
- Haematuria
- Hypertension or hypotension
- Infection
- Myocardial infarction
- Nausea or vomiting
- Pain
- Perforation or dissection of a blood vessel
- Proteinuria
- Stroke
- Retroperitoneal bleeding
- Vascular complications requiring surgery

There are additional risks that could possibly be associated with the tests and procedures performed for the clinical study. These potential risks are described below:
- Risks related to the blood tests required for the study, e.g., excessive bleeding, fainting or light-headedness, haematoma, infection, or the requirement of multiple punctures to locate a vein to draw the sample.

- Risks related to central venous pressure measurement, e.g., infection, irregular heart-beats, collapsed lung, bleeding or death.
- Risks related to radiation; X-ray and CT imaging are required in addition to the routine care. This includes the renal catheterization procedures and the abdominal CT imaging. The additional radiation dose for these tests is limited: The lifetime risk of developing
cancer as a result of an abdominal CT study in a 60-year-old patient is 1:1,300.

No information is available for this procedure and pregnancy, so women who are pregnant are not eligible to participate in this study.

The study may involve unknown or unforeseen side effects or complications other than those mentioned above.

If any complications occur, they may lead to repeat or prolonged hospitalization, repeat procedures, emergency surgery, other emergency procedures, or, in rare cases, death.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patient is 18 years of age or older
2. Patient admitted to the hospital with a primary diagnosis of ADHF who is chronically treated with at least one oral loop diuretic.
3. Patient presents at least two of the following clinical signs of manifest volume overload:
3.1 Jugular venous distension
3.2 Dyspnea, rales, or evidence of pulmonary congestion or oedema on admission chest radiography
3.3 Abdominal discomfort compatible with internal organ congestion and/or hepatomegaly
3.4 Peripheral oedema
4. Ultrasonic evidence of IVC plethora, defined as IVC diameter >2.0 cm.
5. BNP levels >300 pg/dL or NT-proBNP >1500 pg/dL .
6. Evidence of cardiac etiology as per cardiac ultrasonography.
7. LVEF 8. CVP (Invasively measured) >/<= 14 mmHg
9. Male or non-pregnant / non-lactating female (NOTE: Females of child bearing potential must have a negative pregnancy test).
10. Patient understands the nature of the procedure and provides written informed consent prior to any study specific assessments.
11. Patient is willing and able to comply with the specified study requirements and follow-up evaluations, and can be contacted by telephone.

Exclusion criteria

Clinical and general criteria: ;1. INR >3, use of a NOAC in the past 48 hours or contraindication to systemic anticoagulation with Heparin.
2. Evidence of hemodynamic instability, evidence of shock with organ hypoperfusion, or need for inotropic support.
3. Overt pulmonary oedema, or Respiratory insufficiency/hypoxia (peripheral haemoglobin saturation <90% with supplemental oxygen), need for non-invasive positive pressure ventilation or intubation.
4. Severe renal dysfunction (eGFR before decompensation <45 ml/min/1.73 m2 BSA or <25 on admission).
5. Known renal artery stenosis.
6. Known intrinsic kidney disease (e.g., established diagnosis of diabetic nephropathy with macroproteinuria, chronic glomerulonephritis).
7. Severe anaemia (haemoglobin 8. Thrombocytopenia with a platelets count <100,000.
9. Acute coronary syndrome within 4 weeks prior to admission.

10. Active myocarditis or hypertrophic obstructive cardiomyopathy.
11. Complex congenital heart disease.
12. Severe valvular stenosis.
13. Severe morbid obesity (BMI >35).
14. Fluid retention that is not primarily of cardiac origin (e.g., advanced liver disease, severe hypo-albuminaemia, etc.)
15. Temperature > 38°C (oral or equivalent), or sepsis, or active systemic infection requiring IV anti-microbial treatment.
16. Large ascites per ultrasound/CT.
17. Cognitive impairment.
18. Planned PCI, or more than minor surgery in the next 3 months.
19. Moribund patient, or patient with malignancy or other comorbidities limiting life expectancy to less than one year.
20. Patient has a known allergy to Nickel.
21. Contraindication to recommended study medications or intravascular contrast material that cannot be adequately controlled with pre-medication.
22. Concurrent enrollment in another device or drug trial that has not completed the primary endpoint or clinically interferes with the current study endpoints. ;CT Imaging: ;Patient has renal venous anatomy that is unsuitable for device placement for treatment, including:
23. Renal vein length 24. Renal vein diameter /= 16 mm.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-05-2019
Enrollment:	10
Type:	Actual

Medical products/devices used

Generic name:	Transcatheter Renal Venous Decongestion (TRVD) System
Registration:	No

Ethics review

Approved WMO Date:	13-03-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL65757.078.18
Other	Study has been submitted but no NCT number was yet received. This will be provided.