The safety and feasibility evaluation of the Doraya catheter in subjects with Acute Heart Failure

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The objective of this study is to assess the safety and feasibility of the Doraya Catheter in the treatment of subjects hospitalized with congestive AHF, with insufficient response to diuretic therapy.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON46587

Source
ToetsingOnline

Brief title
Doraya FIH Study

Condition

- Heart failures

Synonym
congestive heart failure, with insufficient response to diuretic

Research involving
Human

Sponsors and support

Primary sponsor: Revamp Medical Ltd.
Source(s) of monetary or material Support: industry

Intervention

Keyword: Acute Heart Failure, congestion, Safety, Temporary catheter

Outcome measures

Primary outcome

- Primary Safety: Device or procedure related Serious Adverse Event (SAE) rate through 30 days post index procedure as adjudicated by a Clinical Events Committee (CEC).

- Primary Feasibility: Technical success, defined as ability to position the device below the renal veins, to regulate the flow in the IVC using the device by creating a gradient pressure of at least 2 mmHg, and to withdraw the device.

Secondary outcome

Secondary Observational Measures:

Clinical and observational measures (baseline, during treatment, 24 hours following treatment and at discharge):

* Congestion signs & symptoms: Dyspnea (Likert scale), orthopnoea, pulmonary rales, jugular venous distension and peripheral edema.

* Renal function: Urea, creatinine, eGFR, hourly urine output, daily fluid balance,

daily diuretic dose.

* Circulatory system hemodynamics (during treatment only): Renal Venous Pressure (RVP, continuously measured through the catheter), Right Atrial Pressure (RAP) or Central Venous Pressure (CVP), peripheral venous pressure (PVP), Heart rate

* Using a Swan-Ganz catheter: Cardiac Output, Pulmonary Artery Pressure (PAP),

mixed venous (pulmonary artery) saturation and Pulmonary Wedge Pressure (PWP)

* Clinical measures: Body weight, serum electrolytes, sodium, potassium, BNP/NT-proBNP, blood pressure, length of hospital stay.

* Medical HF therapy including need for intensification of therapy (e.g., mechanical ventilation/therapy, circulatory support with inotropes, use of vasodilators). Clinical and observational measures 7 days, 30 & 60 days after treatment:

* Clinical manifestations of worsening or persistent heart failure as defined by at least one of the following: new, persistent or worsening dyspnea, orthopnea, pulmonary basilar rales/crackles, jugular venous distension.

* Re-hospitalization

Study description

Background summary

Acute heart failure (AHF) is often a life-threatening event requiring urgent medical attention and can mark a transition to a more debilitating phase of the disease. About 1/6 (1M out of 6M in the US) of the HF patients are hospitalized due to AHF each year. Up to 10% of patients with AHF die in hospital and 20*40% die within a year, while 20*25% are readmitted to the hospital within 30 days.

2.1 Importance of Congestion in AHF: diagnosing and therapy guidance
Available data suggest that the main reason for hospitalization for worsening HF is related to the symptoms (dyspnea or breathlessness; leg swelling) of congestion, manifested also by signs [e.g. jugular venous distension (JVD), rales, and edema] of congestion, rather than low cardiac output4. Although congestion is the main reason for hospitalization, many patients are discharged without losing body weight and with persistent signs of congestion. Congestion is associated with a poor prognosis and is an important target for therapy.

2.2 Management of AHF patients (ESC 2016 Guidelines4)
Diuretics are a cornerstone in the treatment of patients with AHF and signs of fluid overload and congestion. Diuretics increase renal salt and water

excretion and additionally have some vasodilatory effect.

The initial approach to congestion management involves I.V. diuretics with the addition of vasodilators for dyspnea relief if blood pressure allows. To enhance diuresis or overcome diuretic resistance, options include dual nephron blockade by loop diuretics (i.e. furosemide or torasemide) with thiazide diuretics or natriuretic doses of MRAs. However, this combination requires careful monitoring to avoid mal effective alterations in potassium levels (hypokaliemia or hyperkaliemia, derived by the type of diuretic agents used) and moreover renal dysfunction and hypovolaemia.

Intravenous vasodilators are the second most often used agents in "Warm" AHF for symptomatic relief; however, there is no robust evidence confirming their beneficial effects. Vasodilators seem to have a negative effect on AHF patients with worsening renal function, manifested in escalation of WRF correlated to the addition of vasodilators to intravenous diuretics compared with intravenous diuretics alone.Thromboembolism prophylaxis with heparin or another anticoagulant is recommended unless contraindicated or unnecessary (because of existing treatment with oral anticoagulants). Use of an inotrope should be reserved for hypotensive AHF patients with a severe reduction in cardiac output resulting in compromised vital organ perfusion, which occurs most often in hypotensive AHF.

2.3 Diuretic Resistance in AHF patients
The mainstay of AHF treatment relies on effective diuretic regime, which mandates functional kidneys (as the target organ for those agents). Inevitably, deterioration in kidney function (manifested by reduced kidney filtration or Glomerular Filtration Rate - GFR), results in diminished efficacy to physiologically regulate fluid status (by altering fluid retention or urination), namely Diuretic resistance.

Diuretic resistance was well proven to independently have clinical importance, manifested in increased mortality and higher re-admission rates10. To date there is no formal guideline to monitor diuretic response4 and the diuretic resistant population still lacks better definition and treatment options.

2.4 Current Management of Diuretic Resistant AHF Patient
The development of Worsening Renal Failure (WRF) in patients with congestion related to AHF is a common but difficult clinical problem to manage as the kidney plays a major role in controlling volume status. The incentive is clear, as the association between impaired or worsening renal function and mortality in patients with AHF strongly suggests the possibility that an effective treatment should improve those patients' outcomes.

Nevertheless, to date there is no single effective approach to the management of this condition, above all, to those patients which have diuretic resistance. Current approach for poor responders to initial dose of diuretics is to

increase dosage and / or to add different type of diuretic until adequate diuresis occurs. Low cardiac output is usually not the main cause for hospitalization and the patients usually present with normal to high blood pressure. The *wet & warm* group targeted by this device is highly associated with persistent volume overload, and many HF patients are discharged with persistent signs and symptoms of congestion and/or a high LV filling pressures as previously mentioned11. Hospital stay for these patients widely varies across the globe: in the US, average length of stay is 6 days (4-10 days for vast majority of patients), with 24% of readmission in 30 days. In Europe, average length of stay is much longer, 7-14 days, with markedly reduced readmission rates to high single digit.

Study objective

The objective of this study is to assess the safety and feasibility of the Doraya Catheter in the treatment of subjects hospitalized with congestive AHF, with insufficient response to diuretic therapy.

Study design

This study is a prospective, single-arm, open label, multi-center first-in-human study designed to evaluate the safety and feasibility of the Doraya Catheter in the treatment of congestive AHF, with insufficient response to standard diuretic therapy.

Intervention

The Doraya is a percutaneously delivered catheter which is deployed over-the-wire using fluoroscopy and positioned in the inferior vena cava, below both renal veins (deployment is similar to IVC filter procedure technique). Once its position is validated using radiopaque markers, the operator deploys the catheter by pulling back the catheter outer shaft. The catheter*s self-expandable nitinol frame will then be opened in the vessel, allowing the operator to control and regulate the flow in the IVC. The guidewire will then be removed to allow monitoring of local hemodynamic pressures (renal and peripheral venous pressures).

The catheter self-expanding Nitinol frame is attached on the distal end of the catheter, and is covered by a polyurethane layer at its the distal end. Manipulation of the distal end of the frame (aperture like configuration) manages the flow, which is monitored by pressure measured through the catheter. While the catheter is deployed in the IVC (up to 24 hours), the operator can use the catheter handle to control the flow in the vessel by constricting or opening the catheter. The distal element of the catheter is partially coated with polyurethane which is coated with passive

hydrophilic material (HydromedTM, Advansource Biomaterials) to prevent cellular adhesion and thrombus formation.
Removal is done under fluoroscopy guidance by insertion of the guidewire, re-mounting the outer shaft on the catheter frame, and removing it from the body. Further information can be found in the Instructions For Use (IFU).
Detailed training on device handling, IFU and IB, covering instructions on catheter insertion, operation and withdrawal, will be provided by the Sponsor to each performing physician during a Site Initiation Visit.

Study burden and risks

Tekst directed to the patient:
You may experience side effects while being in the study. Because this is the first time that the Doraya catheter is used in humans, in addition to the risks described below, there may also be risks or side effects that are unknown at this time. Everyone taking part in the study will be watched carefully for any side effects. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Some side effects may go away after treatment with the Doraya is stopped. In some cases, side effects can be serious, long lasting or may never go away. There also is a risk of death.

In this study you are required to undergo two (2) catheterization procedures, which in rare cases can cause pain or discomfort during catheter insertion, and later because of prolonged laying down. There is a possibility, while injecting contrast solution that you feel discomfort around your ribcage, or feel a sense of heat. However, these sensations usually pass after a few seconds.
The risks that may be associated with the Doraya treatment are listed below, divided to potential risks during catheter insertion, during the temporary procedure and following the removal of the catheter.
Risks during insertion of the Doraya catheter include:
* Misplacement of the device may occur during insertion. Highly unlikely, but will require the investigator to re-position the device during catheterization.
* Leakage of contrast media from the normal intravascular compartment into surrounding soft tissue - is highly unlikely and may prolong the initiation of the procedure.
* Injury to the Inferior Vena Cava: Minor injury is expected in most cases, similar to other vascular interventions. Perforation or penetration are of very low likelihood, but will require a medical attention.
* Air embolization is a small air bubble that may reach the lungs during the catheter insertion, similar to other venous interventions. Low likelihood with a minor clinical risk.
Risks during procedure:
* Risks to the heart include:
- Arrhythmia (changes in heartbeat)
- Significant drop in blood pressure may happen due to full occlusion of the blood flow. While unlikely, they will require immediate medical attention.

* Risks to the lungs include:
- Thrombosis or embolization, the formation of blood clots in the veins or on the device, may occur during procedure and may reach the lungs. As the procedure includes various anti thrombotic treatment it is unlikely, but will require medical attention to prevent long term effect.
* Risks to the insertion site include:
- Infection and thrombosis (formation of blood clot at the site) are highly unlikely, and will require an immediate medical attention.
- Hematoma, collection of blood outside the blood vessels, is a common complication of catheters. While of low clinical risk, it will require medical attention.
- Low local pain is associated with catheters. While of low clinical risk, it will require medical attention.
* Systemic risks include:
- Leg Ischemia (poor blood supply) and/or leg swelling may occur during the procedure due to limiting blood back flow to the heart, and are associated with pain. These conditions, while of low clinical risk, will require medical attention.
- Thrombocytopenia is a condition characterized by abnormally low levels of thrombocytes, also known as platelets, in the blood. Highly unlikely to occur, and will require medical attention
- Excessive procedural and post procedural bleeding are highly unlikely to occur, and will require immediate medical attention
- Worsening of Heart Failure symptoms
- Death

Other currently unknown risks and discomforts could appear. It is therefore very important that any new health problem is quickly reported to the investigator, regardless of whether or not you think it has to do with the study.
Throughout the course of the treatment, your doctor will watch your progress closely, and will adjust your medicines as needed. If your doctor decides that the Doraya catheter is unsuccessful at any point in time, he will stop the treatment and offer you other choices for your treatment and care. Your doctor will discuss this with you.

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) Subject is >18 and <85 years of age.
2) Subject is hospitalized with primary diagnosis of congestive AHF.
3) Evidence of fluid overload as indicated by 2 or more of the following criteria:
a) peripheral edema *2+
b) jugular venous distension *7 cm H2O
c) radiographic pulmonary edema or pleural effusion
d) enlarged liver or ascites
e) pulmonary rales or paroxysmal nocturnal dyspnea, or orthopnea.
4) Subject insufficiently responds to standard diuretic therapy, meeting the following criteria:
Sufficient diuretic treatment:
a) >80 mg furosemide per day or an equivalent, or;
b) >1.5X of the subject chronic baseline diuretic level
With at least of one of the following:
a) reduction of <1 Kg/day in subject weight, or;
b) <1ml/kg/hour Urine output (for a duration of at least 4 hours), or;
c) IVC with no inspiratory collapse by cardiac ultrasonography
5) Brain natriuretic peptide (BNP) *400 pg/mL or N-terminal-pro-brain natriuretic peptide (NT-proBNP) *1,600 pg/ mL.
6) Subject understands the nature of the procedure and provides written informed consent prior to any study specific assessments.
7) Subject is willing and able to comply with the specified study requirements and follow-up

assessments, and can be contacted by telephone.
8) Evidence of cardiac etiology as per cardiac ultrasonography.
9) IVC with no inspiratory collapse by cardiac ultrasonography.
10) Urine output <1ml/kg/hour, for minimum duration of 4 hours, preferably measured through a urinary catheter.
11) CVP>12 mmHg confirmed at the beginning or prior to the catheterization procedure.

Exclusion criteria

1) Systolic blood pressure <90 mmHg at the time of screening.
2) Acute myocardial infarction or acute coronary syndrome within past 7 days.
3) Known LVEF < 10% by echocardiography within 1 year prior to enrolment.
4) Complex congenital heart disease (e.g. Tetralogy of Fallot subjects, single ventricle physiology).
5) Known active myocarditis, hypertrophic obstructive cardiomyopathy, constrictive pericarditis or cardiac tamponade.
6) Severe Aortic valvular disorder (i.e., hemodynamically relevant valvular diseases such as severe stenosis\severe regurgitation) or Severe mitral disease with planned intervention.
7) Severe renal dysfunction (eGFR <18 ml/min/1.73 m2 BSA) or subject is on chronic dialysis.
8) Subject has history of deep vein thrombosis and/or pulmonary embolism
9) Evidence of cardiogenic shock with organ hypo-perfusion.
Current or need of mechanical support (intra-aortic balloon pump, endotracheal intubation, mechanical ventilation, or any ventricular assist device),
10) Subject with bleeding disorder which limit the use of antiplatelet and/or anticoagulant therapy (e.g. Thrombocytopenia with platelets count <100,000, anemia with hemoglobin <9 mg/dL)
11) Subjects with a known infra-renal IVC diameter of <14mm
12) Open or infected wounds in the legs.
13) Subject is pregnant or lactating. Pregnancy confirmed by positive urine or serum test.
14) Subject with advanced liver disease or serum Albumin<2.5 g/dL
15) Evidence of active systemic infection (documented by either one of the following: fever >38°C, ongoing uncontrolled known infection (i.e. inflammatory parameters not decreasing despite * 48 hrs of antibiotic treatment)
16) Severe obesity (BMI >35).
17) Subject with known hypersensitivity to Nickel.
18) Subject with history of radiation therapy to lower abdomen.
19) Contraindication to recommended study medications or intravascular contrast material that cannot be adequately controlled with pre-medication.
20) Moribund subject or subject with severe or deteriorating damage in more than 3 critical body systems or requiring inotropic therapy for survival.
21) Concomitant disease expected to cause death in * 90 days
22) Any other medical, social, or psychological issues that in the opinion of the investigator preclude the subject from receiving this treatment, or the procedures and evaluations pre- and post-.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Generic name:	Doraya catheter
Registration:	No

Ethics review

Approved WMO

Date:	20-07-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	NL63504.100.17