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A prospective comparison of alginate-hydrogel with standard medical therapy to determine impact on functional capacity and clinical outcomes in patients with advanced heart failure (AUGMENT-HF trial)

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Aims	AUGMENT-HF was an international, multi-centre, prospective, randomized, controlled trial to evaluate the benefits and safety of a novel method of left ventricular (LV) modification with alginate-hydrogel.
Methods	Alginate-hydrogel is an inert permanent implant that is directly injected into LV heart muscle and serves as a prosthetic scaffold to modify the shape and size of the dilated LV. Patients with advanced chronic heart failure (HF) were randomized (1 : 1) to alginate-hydrogel ($n = 40$) in combination with standard medical therapy or standard medical therapy alone (Control, $n = 38$). The primary endpoint of AUGMENT-HF was the change in peak VO_2 from baseline to 6 months. Secondary endpoints included changes in 6-min walk test (6MWT) distance and New York Heart Association (NYHA) functional class, as well as assessments of procedural safety.
Results	Enrolled patients were 63 ± 10 years old, 74% in NYHA functional class III, had a LV ejection fraction of $26 \pm 5\%$ and a mean peak VO_2 of 12.2 ± 1.8 mL/kg/min. Thirty-five patients were successfully treated with alginate-hydrogel injections through a limited left thoracotomy approach without device-related complications; the 30-day surgical mortality was 8.6% (3 deaths). Alginate-hydrogel treatment was associated with improved peak VO_2 at 6 months—treatment effect vs. Control: $+1.24$ mL/kg/min (95% confidence interval 0.26–2.23, $P = 0.014$). Also 6MWT distance and NYHA functional class improved in alginate-hydrogel-treated patients vs. Control (both $P < 0.001$).
Conclusion	Alginate-hydrogel in addition to standard medical therapy for patients with advanced chronic HF was more effective than standard medical therapy alone for improving exercise capacity and symptoms. The results of AUGMENT-HF provide proof of concept for a pivotal trial.

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Introduction

Heart failure (HF) is a major health problem worldwide with 5-year mortality rates that exceed 50%.[1] As HF progresses, the heart undergoes progressive left ventricular (LV) remodelling. According to the principle of Laplace's law, as the LV dilates and LV wall thins, and wall stress increases, resulting in continued myocardial damage. Unless an intervention can break this deleterious spiral of events, HF will continue to progress with worsening LV dilation. Left ventricular remodelling is maladaptive and its progression contributes to worsening of clinical symptoms, marked exercise intolerance, and congestion, all of which culminate in hospitalizations due to HF decompensation and premature death of the afflicted patient.

Despite recent advances in therapy, morbidity and mortality resulting from HF remain unacceptably high.[2] The use of tissue engineering principles to improve myocardial functionality has shown encouraging preclinical results.[3–5] The concept of LV modification or restoration with the intra-myocardial injection of an alginate-based polymer results in increased wall thickness and a change of LV geometry.[6] In a canine model of HF, LV injection/implantation with an alginate-based formulation led to improvement in indexes of LV systolic function without negatively impacting LV relaxation or filling.[7] In a prior clinical study evaluating the safety and feasibility of alginate-hydrogel administered at the time of cardiac bypass surgery, there were observations of an increase in LV wall thickness, reduction of end-diastolic volume, and end-systolic volume as well as decreases in myocardial wall stress at end-diastole and end-systole over 3–6 months.[8]

The AUGMENT-HF clinical trial was designed to evaluate the benefits and safety of treatment with alginate-hydrogel in patients with advanced chronic HF.

Methods

Study design and protocol

AUGMENT-HF was an international, multi-centre, prospective, randomized, controlled clinical trial of alginate-hydrogel in patients with advanced chronic HF. Eligible patients were randomly allocated to receive either alginate-hydrogel in addition to standard medical therapy or standard medical therapy alone (Control). Randomization was stratified for two variables: aetiology of cardiomyopathy (ischaemic vs. non-ischaemic) and baseline peak VO_2 (greater than or ≤ 12.5 mL/kg/min). The study included patients aged 18–79 years, who had a peak VO_2 of 9.0–14.5 mL/kg/min, a left ventricular ejection fraction (LVEF) $\leq 35\%$, a left ventricular end-diastolic dimension indexed to body surface area of 30–40 mm/m^2, and were required to be on stable, evidence-based therapy for HF. Primary exclusion criteria were an LV wall thickness <0.8 cm (mid-ventricular level), a serum creatinine

>2.5 mg/dL, clinically significant liver enzyme abnormalities, Q-wave myocardial infarction (MI) within the last 30 days, or a history of stroke within 60 days.

Core laboratories, blinded to treatment assignment, conducted the evaluation of key measures of cardiopulmonary exercise (CPX) testing (peak VO_2), cardiac imaging (echocardiography), Holter monitors, and laboratory evaluations. Blinded endpoint assessment was used to compensate partially for the fact that the trial could not be truly double blind. Sham thoracotomy and intra-myocardial injection (with no prospect of improvement) in the control patients were not considered ethically acceptable. We used, as the basis for the primary endpoint peak VO_2, which is objective in as much as it measures an objective physiological variable, recognizing it remains subject to bias in the form of differential effort during exercise testing, in that the patient knows whether or not he/she had undergone surgery. We measured peak achieved respiratory exchange rate (RER) as a measure of exercise effort, to assess if the randomized groups would demonstrate any differential effort in follow-up exercise tests. An independent clinical events committee (CEC) adjudicated all events suggestive of study endpoints, including major adverse cardiac events (MACE), whilst blinded to treatment group allocation. Major adverse cardiac events were defined as cardiac death, cardiac arrest, MI, sustained ventricular arrhythmias, pulmonary oedema, acute HF, unstable angina, and major bleeding. A Data Safety Management Board provided an independent ongoing assessment of safety.

The study was conducted at 14 centres in Australia, Germany, Italy, the Netherlands, and Romania. The protocol was approved by the regulatory authorities in each country and the local Ethics Committees. The study was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and local and national regulations. Written informed consent was provided by all patients.

The trial protocol defined an initial study report on efficacy (exercise tolerance) to be generated after every patient had been followed for a minimum of 6 months and a final 'extended follow-up phase' study report focusing on long-term safety after 24 months follow-up. First enrolment occurred in May 2012, and enrolment was completed in April 2014. This paper provides the report on the primary results analyses for 6 months of follow-up.

Investigations

After signing informed consent, each patient underwent a baseline screening assessment including CPX testing and assessment of 6-min walk test (6MWT) distance. In addition, at specific visits echocardiography assessments were performed, quality-of-life questionnaires were completed, and safety blood samples were taken. To investigate for potential ventricular ectopy, 24-h-Holter monitoring was performed at screening as well as 3 and 6 months. Holter recordings were digitally stored and assessed by central blinded review (BioClinica Cardiovascular Safety Services).

Patients were required to perform two CPX tests within 30 days of randomization and performed at least 20 h apart that differed by no

>15% in the observed value for peak VO_2 (as per Core laboratory report). Cardiopulmonary exercise could be repeated a third time, if needed. Patients meeting the entry criteria (based on the mean of the last two assessments) were randomized to alginate-hydrogel or Control.

Training on standardized procedures for conduct of CPX testing and validation testing were required for each clinic prior to study initiation. Revalidation was required every 6 months. Cardiopulmonary exercise data were uploaded to the blinded core lab for analysis and the core laboratory provided rapid feedback on test quality for each test. Analyses of CPX measures were determined from averaged 10 s gas exchange data from the start to the end of exercise. Patients returned to the clinic at 3 and 6 months post-discharge for follow-up evaluations. Patients were required to complete one CPX test at 3 months, and two CPX tests at the 6 months (with the average value for these two tests being employed in analyses).

Therapy

Patients randomized to the investigational device group had alginate-hydrogel (calcium-alginate-hydrogel) administered during a surgical procedure as previously described.[8] The approximate locations of alginate-hydrogel injections and technical details are presented in *Figure 1*.

Statistical methods

The primary efficacy endpoint in this study was the change in peak VO_2 from baseline to 6 months. The primary safety objective was to estimate the 30-day mortality associated with the implantation of alginate-hydrogel. Six-minute walk test distance, quality of life as measured by Kansas City Cardiomyopathy Questionnaire (KCCQ), patient global assessment (PGA), New York Heart Association (NYHA) functional class, CPX measures of peak watts and total exercise time, and measures of echocardiographic imaging were all pre-specified secondary endpoints. Statistical significance was attached to P-values of <0.05 (SAS version 9.3; SAS institute).

Data analysis were performed according to intention to treat. The primary and secondary efficacy analyses were performed on the modified intention-to-treat (mITT) analysis population, which included all randomized patients (Control group) and for the alginate-hydrogel group, all patients randomized to the alginate-hydrogel group for whom the surgery to implant the alginate-hydrogel device was started. The safety analysis dataset comprised all randomized patients. No imputation was performed for missing data.

To test the group differences for the primary outcome, a repeated-measures mixed model was used with an unstructured covariance matrix to model the within-patient variability. The same model was used to test the group differences for echocardiographic imaging results and KCCQ data. It was pre-specified that non-normally distributed data were to be analysed using non-parametric testing, which was the case for 6MWT distance. The treatment effect for NYHA functional class at 6 months was compared by means of logistic regression with ordinal polytomous response adjusted for baseline.

Cumulative survival curves for the time-to-event analyses were constructed according to the Kaplan−Meier method and differences were examined by the log-rank statistic. The Cox proportional hazards regression (SAS proc phreg procedure) was used to estimate the hazard ratios with treatment as the only covariate. Event rates were expressed as the percentage of events per 100 patient-years of follow-up, taking into account the censoring of follow-up data. The repeated-measures analysis for categorical variables was done using the SAS proc logistic procedure including terms for treatment and baseline value.
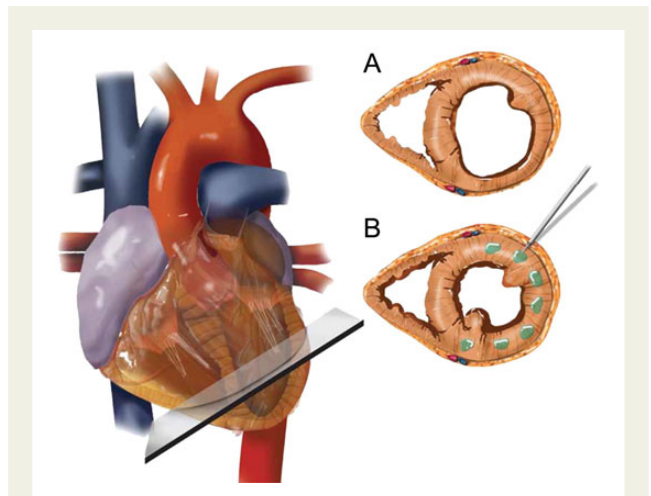

Figure 1 Algisyl-LVR implantation. Standardization of the placement of the implants at the mid-ventricular level identified as the halfway point between the left ventricular base (defined as the atrioventricular groove) and apex (*A*). The implants are equally spaced in the mid-myocardium starting at the antero-septal groove and ending at the postero-septal groove (*B*). Note: alginate-hydrogel (LoneStar Heart, Inc., Laguna Hills, CA, USA) is a proprietary calcium-alginate-hydrogel that consists of two components: an Na^+-alginate component supplied as a sterile aqueous solution with 4.6% mannitol and a Ca^{2+}-alginate component consisting of water insoluble particles suspended in a sterile 4.6% mannitol solution. These two components are mixed immediately before use, and then combined in one syringe for delivery as intra-myocardial injections. Alginate-hydrogel is administered during a surgical procedure. A left thoracotomy is performed to expose the heart and the pericardium. The left ventricular free wall was identified and the injection sites marked with a surgical marker. In total, 10−19 intra-myocardial injections were made on the beating heart, circumferentially, at the left ventricular mid-ventricular level halfway between the left ventricular apex and base starting at the antero-septal groove and ending at the postero-septal groove. Left ventricular wall thickness must not have been <8 mm at the locations where the alginate-hydrogel was to be injected. The total number of injections administered for an individual patient depended on the size of the heart (amount of space available on the LV-free wall). All injections were made along or within ∼1 cm of a single mid-ventricular line, being careful to avoid any visible coronary vasculature. Standardization of the placement of the implants was performed via the identification of standard anatomical features (atrioventricular groove and apex). Injections of 0.3 mL of alginate-hydrogel were separated by ∼0.5−1 cm and made at the mid-wall depth of the myocardium.

The primary safety endpoint for the study was 30-day all-cause mortality in patients randomized to alginate-hydrogel for whom the alginate-hydrogel device was implanted. The starting point for the 30-day count was the start of surgery. The 30-day all-cause mortality associated with the implantation of the alginate-hydrogel device was to be qualitatively compared with the observed rate of 5%, estimated based upon three recently completed clinical trials that investigated similar patient populations and evaluated surgical ventricular reconstruction or the CorCap device.[9,10] Assuming the 30-day mortality rate is consistent with the estimated 5% rate and a sample size of $N = 38$, the estimate was that the

observed mortality in this study would be between 0.1 and 17.4% with 95% confidence (calculations performed using PASS 2008 and the Exact (Clopper Pearson) confidence interval formula). Based on the binomial distribution, a sample size of 38 patients, and a probability of post-surgical mortality equal to 5%, the probability of observing four or fewer deaths was 96.0%. The probability of observing five or more deaths was 4.0%.

Results

In total, 113 patients were screened for the study, and 35 patients were found to be ineligible or declined participation at screening. A total of 78 patients were randomized (1 : 1) to alginate-hydrogel ($n = 40$) and Control ($n = 38$). The procedure to implant the alginate-hydrogel device was not performed in five patients randomized to this treatment group. Two of these patients were found to have a LV thrombus (echocardiography) on the day prior to the planned surgical procedure and deemed therefore ineligible. Three patients withdrew consent after randomization to the alginate-hydrogel group and prior to the surgical procedure. All other patients randomized to the alginate-hydrogel ($n = 35$) underwent a successful surgical procedure to implant the device; there were no failures to implant the device.

Demographics and baseline characteristics for the mITT population are summarized in *Table 1*. All baseline characteristics were comparable between groups. The patients enrolled showed significant LV dysfunction and significantly reduced functional capacity with a mean LVEF of 26 ± 5%, and a mean peak VO_2 of

Table 1 Baseline demographics

	Alginate-hydrogel ($n = 35$)[a]	Control ($n = 38$)
Age (years)	63.1 ± 10.1	62.1 ± 9.2
Male	27 (77%)	34 (90%)
Ethnicity (white)	35 (100%)	38 (100%)
Ischaemic HF	20 (57%)	22 (58%)
Non-ischaemic HF	15 (42.9%)	16 (42.1%)
NYHA functional class (mean)	2.9 ± 0.4	2.8 ± 0.5
Class II/III/IV	5/28/2	9/26/3
LVEF (%)	25.4 ± 5.3	25.6 ± 5.0
Peak VO_2 (mL/kg/min)	12.1 ± 1.8	12.2 ± 1.8
6MWT distance (m)	275 ± 86	310 ± 80
Mitral regurgitation $\geq 3+$	15 (43%)	22 (58%)
Hypertension	20 (57%)	23 (61%)
Diabetes	12 (34%)	17 (45%)
Atrial fibrillation	16 (40.0%)	37 (47.4%)
Stroke (CVA)	4 (11%)	5 (13%)
Prior myocardial infarction	22 (55.0%)	39 (50.0%)
Previous PCI or CABG	9 (26%)	11 (29%)
CRT	5 (14%)	5 (13%)
ICD	10 (29%)	9 (24%)

Control, standard medical therapy alone; *n*, number of patients; 6MWT, 6-min walk test; HF, heart failure; CVA, cardio vascular accident; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.
[a]Modified intention-to-treat population; data are mean $\pm$ SD or patients (%).

12.2 ± 1.8 mL/kg/min. Baseline concomitant HF medications are summarized in *Table 2*.

For the patients undergoing the alginate-hydrogel procedure, the mean procedure duration was 81 ± 25 min, ranging from 50 to 160 min. The median ICU length of stay (LOS) was 2 days and median hospital LOS was 15 days. The mean number of intra-myocardial implants/injections for patients undergoing the alginate-hydrogel procedure was 16 ± 2, ranging from 11 to 19 (*Table 3*).

Cardiopulmonary exercise testing

Mean peak VO_2 gradually increased over time in patients in the alginate-hydrogel group while it remained unchanged in the Control group (*Figure 2*A). Alginate-hydrogel treatment was associated with improvement in peak VO_2 compared with Control treatment; the mean treatment effect was an increase of 1.24 mL/kg/min (95% confidence interval, CI 0.26–2.23, $P = 0.014$).

The improvement in peak VO_2 was accompanied by a 1.0 min ($P = 0.001$) improvement in total treadmill exercise time (*Figure 2*B) and a 10 W improvement in maximum workload ($P < 0.001$). The peak exercise RER remained unchanged over time from baseline (1.02 ± 0.09) to 3 months (1.03 ± 0.12) and 6 months (1.02 ± 0.11).

In subgroup analyses, neither aetiology of HF (ischaemic vs. non-ischaemic; *P*-value for interaction 0.066) nor baseline peak VO_2 (greater than or ≤ 12.5 mL/kg/min; *P*-value for interaction 0.23) had a significant interaction for treatment effect. Also for 15 pre-specified subgroups analysed, there were no significant treatment-by-subgroup interactions for the primary endpoint with the exception of the subgroups of patients split by median 6MWT distance at baseline (*P*-value for interaction 0.014). Regional analysis did not find a significant interaction for treatment effect; results were the same for patients from Romania ($n = 45$) compared with patients from all other countries ($n = 28$).

Six-minute walk test distance

Mean 6MWT distance increased over time in patients in the alginate-hydrogel group while mean 6MWT distance remained

Table 2 Concomitant heart failure and cardiac medications at baseline

	Alginate-hydrogel ($n = 35$)	Control ($n = 38$)
Diuretics	34 (97%)	38 (100%)
β-Blockers	33 (94%)	37 (97%)
ARB/ACEi	30 (86%)	35 (92%)
Mineralocorticoid receptor antagonists	26 (74%)	25 (66%)
Anti-thrombotics or anti-platelet agents[a]	34 (97%)	38 (100%)
Anti-platelet aggregation agents[a]	27 (77%)	21 (55%)
Anti-coagulant[a]	17 (49%)	24 (63%)
Lipid lowering	25 (71%)	27 (71%)

Data are number of patients.
Control, standard medical therapy alone; *n*, number of patients.
[a]Not mutually exclusive.

Table 3 Summary details of operative procedure and index hospitalization

	Alginate-hydrogel (n = 35)[a]
Procedure duration (min)	
Mean (SD)	80.5 (24.9)
Median (min−max)	78 (50−160)
Anesthesia duration (min)	
Mean (SD)	190 (29)
Median (min−max)	184 (120−240)
Total number of alginate-hydrogel implants (injections)	
Mean (SD)	15.5 (2.0)
Median (min−max)	15 (11−19)
Total volume administered (mL)	
Mean (SD)	4.6 (0.6)
Median (min−max)	4.5 (3.3−5.7)
ICU length of stay (days)	
Mean (SD)	4.3 (7.3)
Median (min−max)	2 (1−43)
Hospital length of stay (days)	
Mean (SD)	18.4 (13.0)
Median (min−max)	15 (7−65)

Control, standard medical therapy alone; n, number of patients; SD, standard deviation; min, minimum; max, maximum; perc, percentile; ICU, intensive care unit; Index surgical procedure, procedure to implant the alginate-hydrogel device.
[a]Modified intention-to-treat population.

unchanged or declined for patients in the Control group ($P < 0.001$, change in median 6MWT distance +141 m, *Figure 3*).

New York Heart Association assessment

The NYHA functional class at 6 months was improved in the Algisyl group, with 84% having an NYHA functional class I or II, when compared with 26% in the Control group (odds ratio for improvement by one class: 30.2; 95% CI 5.7−160.5, $P < 0.001$, *Figure 4*).

Quality of life

There were no statistically significant differences between groups for any of the 10 KCCQ domain scores (*Table 4*). The self-reported PGA at 6 months was improved in the Algisyl group with >55% of patients reporting that they were much or moderately improved, when compared with 28% of patients in the placebo group (odds ratio for being in a better rank, 3.2; 95% CI 1.2−8.6, $P = 0.019$).

Echocardiographic findings

Echocardiograms were performed at baseline and again at 3 and 6 months. While a majority of patients had an interpretable pre- and post-study, there was a significant amount of missing data due to various technical limitations for many studies. There were no

statistically significant differences between treatment groups for any of the echocardiographic measures (*Table 5*).

Safety profile

In total, three deaths occurred during the 30-day period after the surgical procedure to implant the alginate-hydrogel device. The 30-day absolute mortality rate was 8.57% (95% CI: 1.80−23.06%). The 30-day absolute mortality rate in the Control group (no surgery) was 0%. The major surgical complication rate for the alginate-hydrogel device procedure was 25% (safety population).

The overall incidence of serious adverse events (SAEs) through 6 months of follow-up was not significantly different between the alginate-hydrogel and Control group (*Table 6*). There were also no statistically significant differences between treatment and control for any of the categories of SAEs by body system or preferred term. The incidence of SAEs of Cardiac Disorders was generally reported to be more common among patients in the Control group compared with patients in the alginate-hydrogel group.

Overall, MACE, excluding the index hospitalization, were lower for patients receiving alginate-hydrogel and appears to be due to substantially lower rates of worsening HF and sustained ventricular arrhythmias in patients receiving the alginate-hydrogel device. The incidence of CEC adjudicated secondary safety endpoints and MACE are summarized in *Tables 7* and *8*. The study was not powered to detect differences in either overall MACE or specific categories of events. The listing of causes for non-heart failure hospitalizations is provided in *Table 10*.

Analysis of 24-h-Holter monitors demonstrated no statistically significant differences between groups for measures of supraventricular or ventricular ectopy. There was no increase in ventricular arrhythmias observed for patients receiving alginate-hydrogel.

Discussion

A large number of patients have symptomatic HF, despite the use of all available guideline recommended treatments.[11] The therapeutic options for patients with advanced HF who have become refractory to the currently available medical therapies (pharmacologic and device) are limited;[12] there is an unmet need for new therapeutic options for this growing patient population.[13]

The AUGMENT-HF trial provides the first evidence that surgical treatment with alginate-hydrogel in addition to standard medical therapy was more effective than standard medical therapy alone for improving exercise capacity and symptoms in patients with advanced HF. The results of AUGMENT-HF provide proof of concept that intracardiac injection of alginate-hydrogel leads to beneficial effects in patients with advanced chronic HF and hence warrant further studies to validate the observed effects and to extend them in greater and possibly broader study populations with longer follow-up.

The baseline demographics for the study population represent a group of patients with advanced chronic HF that is very well treated. It is rare in clinical trials of ambulatory HF patients, that the patients studied show a mean peak VO_2 at baseline that is as low as 12.2 mL/kg/min, with all patients having values of 14.5 mL/kg/min or less. These results are based on the average of two qualifying maximum exercise tests, and hence are not the result of a possible underperformance during the learning curve experience of patients.
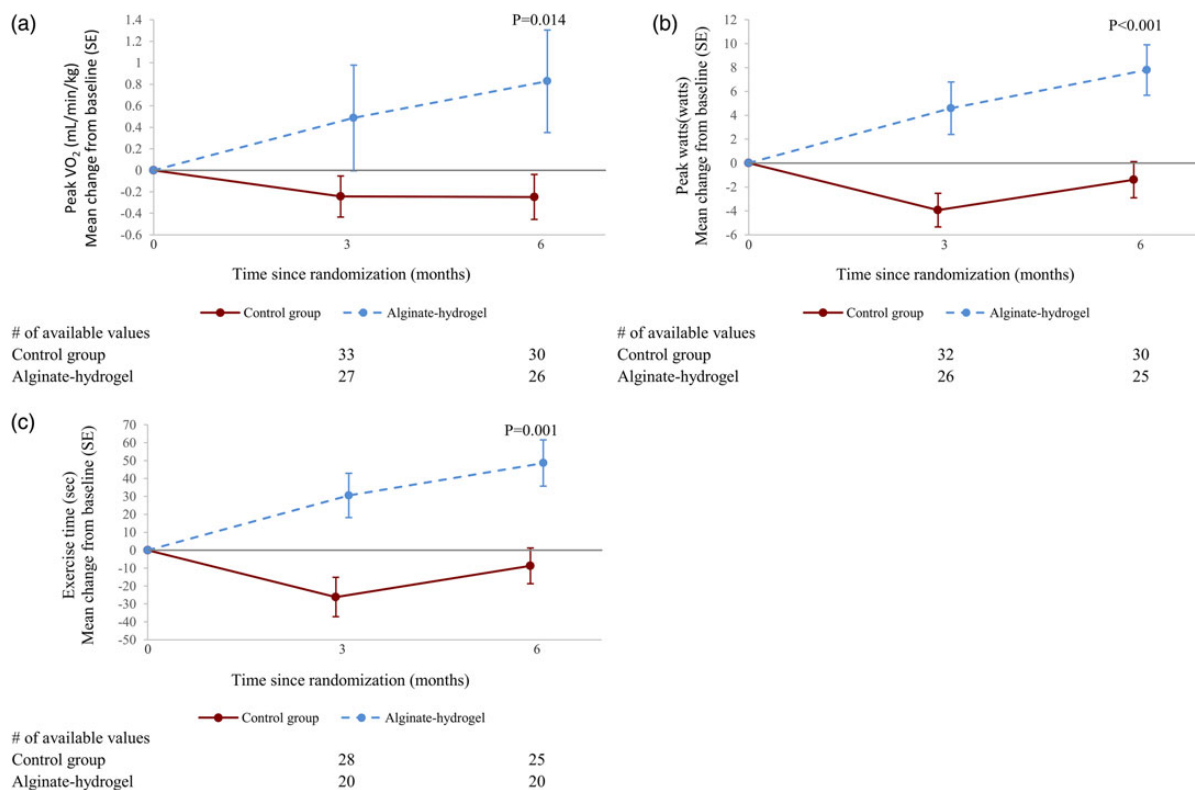
Figure 2 (*A*) Peak VO$_2$ at 6 months: mean change (from baseline). (*B*) Peak watts at 6 months: mean change (from baseline). (*C*) Maximum exercise time at 6 months: mean change (from baseline). Control, standard medical therapy; SE, standard error; *P*-value, (adjusted) mean product effect.
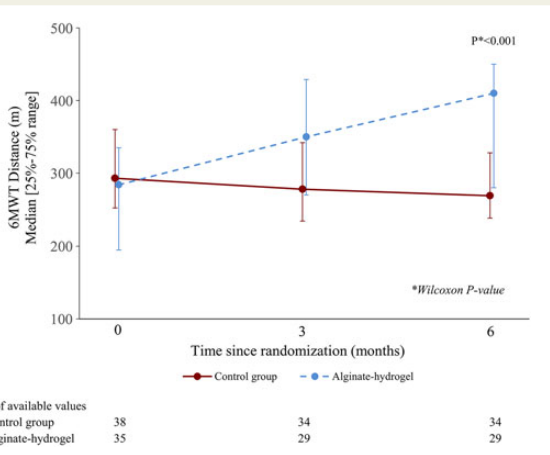

Figure 3 Six-minute walk test distance at 6 months. Control, standard medical therapy; 6MWT, 6-min walk test.

We consider the treatment effect of 1.24 mL/kg/min for changes in peak VO$_2$ over 6 months as an important observation for this patient population. It represents a 10.2% improvement over baseline. Sarullo *et al.* reported that clinically stable HF patients with a peak

VO$_2$ <12.2 mL/kg/min had a 1-year cardiovascular mortality of 66% and a 1-year cardiovascular hospitalization rate of 63%, while patients with a peak VO$_2$ >12.2 mL/kg/min had rates of only 34 and 37%, respectively.[14] Swank *et al.* reported that for every 6% increase in peak VO$_2$ there was an 8% reduction in cardiovascular mortality or HF hospitalization and a 7% reduction in all-cause mortality.[15] In this context, it is interesting that a secondary per-protocol analysis found that alginate-hydrogel provided an improvement in peak VO$_2$ compared with patients in the Control group with a mean treatment effect of 1.59 mL/kg/min (*P* = 0.002).

It is an interesting observation that the mean 6MWT distance in the alginate-hydrogel group at baseline was substantially below the 300 m threshold and was observed to increase above the 300 m threshold at the 3- and 6-month follow-up visits. Several studies have demonstrated that a 6MWT distance of <300 m is strongly prognostic of subsequent mortality and hospital admission in stable chronic HF[16,17] and in patients with advanced HF.[18] Many consider that an improvement of >50 m in 6MWT distance is clinically very meaningful,[19,20] and changes between 30 and 50 m for 6MWT distance are also often considered clinically relevant.[21] The improvement of 6MWT distance for alginate-hydrogel-treated patients in AUGMENT-HF was >100 m, and hence was an interesting finding. Still, this finding needs to be validated.

Table 4 Mean (Kansas City Cardiomyopathy Questionnaire) scores and changes from screening values

KCCQ domain	Visit	Alginate-hydrogel		Control		P-value between groups
		n	Mean ± SD	n	Mean ± SD	
Overall summary	Baseline	35	47 ± 21	37	49 ± 22	
	6-month	29	65 ± 25	34	60 ± 23	0.12
Clinical summary	Baseline	35	52 ± 21	37	55 ± 22	
	6-month	29	69 ± 26	34	64 ± 21	0.14
Quality of life	Baseline	35	39 ± 27	37	42 ± 26	
	6-month	29	63 ± 27	34	54 ± 26	0.066
Total symptom	Baseline	35	58 ± 22	37	61 ± 25	
	6-month	29	74 ± 26	34	68 ± 22	0.11
Social limitation	Baseline	35	45 ± 27	36	45 ± 28	
	6-month	28	60 ± 32	33	58 ± 28	0.46
Self-efficacy	Baseline	35	71 ± 25	37	78 ± 18	
	6-month	28	80 ± 21	34	79 ± 18	0.16
Symptom burden	Baseline	35	60 ± 23	37	61 ± 25	
	6-month	29	74 ± 26	34	68 ± 22	0.22
Symptom frequency	Baseline	35	55 ± 24	37	62 ± 25	
	6-month	29	74 ± 28	34	67 ± 24	0.079
Symptom stability	Baseline	34	52 ± 21	37	52 ± 27	
	6-month	29	61 ± 22	34	48 ± 25	0.072
Physical limitation	Baseline	35	47 ± 21	37	48 ± 25	
	6-month	29	64 ± 27	34	61 ± 24	0.31

Control, standard medical therapy alone; n, number of available values; SD, standard deviation.

The improvements in peak VO$_2$, 6MWT, and NYHA class in AUGMENT-HF provide a demonstration of a possible clinical benefit for the alginate-hydrogel device treatment. The results provide proof of concept for this new treatment approach. The results require validation and extension in larger patient cohorts that are followed for longer periods of times. A pivotal trial to this end is in the planning phase.

The alginate-hydrogel implant acts as a permanent prosthetic scaffold that aims to reduce wall stress, and prevent further LV enlargement based on the physical principles described in Laplace law. Previously, surgical ventricular restoration (SVR) and devices employing LV reshaping strategies were evaluated in clinical studies such as the STICH trial[25] the ACORN trial[9] of the CorCap device (Acorn) and the PEERLESS-HF trial[22] of the HeartNet device (Paracor Medical Inc.). The goals of SVR were to reduce the increased radius of curvature present in a dilated heart, and both the CorCap and HeartNet devices aimed to restrict and reverse LV dilatation; however, neither of these devices were approved for clinical use and the large multi-centre STICH trial failed to demonstrate a clinical benefit of SVR combined with CABG compared with CABG alone. More recently, other LV reshaping approaches include the Parachute device (Cardikinetix)[23] to reduce the size of the LV cavity with an insert and the Revivent device (Bioventrix)[24] to isolate big dysfunctional regions of the LV. Results from controlled randomized intervention trials are not yet available for these.

The procedural success of the alginate-hydrogel injection approach was 100% in this trial. The mean operative procedure
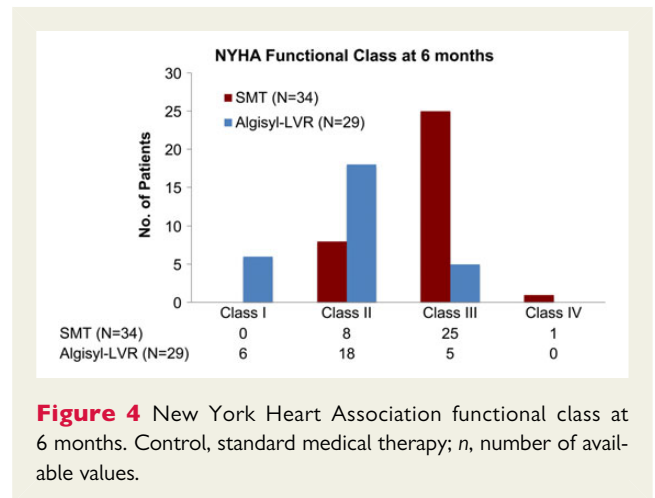

Figure 4 New York Heart Association functional class at 6 months. Control, standard medical therapy; n, number of available values.

time of 80.5 min demonstrated that in most patients the alginate-hydrogel device is implanted with relative ease in the context of a limited surgical procedure. These procedure metrics compare favourably with many current commonly performed 'non-surgical' procedures performed in patients with advanced structural heart disease. This is an important consideration, since both prolonged operative time and anaesthesia time are associated with increased rates of complications. The overall hospital LOS was longer than expected with a median of 15 days. However, there was no

Table 5 Transthoracic echocardiogram mean (standard deviation) values and changes from screening values for selected parameters

	Visit	Alginate-hydrogel		Control		P-value between groups
		n	Mean ± SD	n	Mean ± SD	
LVEDD (cm)	Baseline	33	6.3 ± 0.40	34	6.4 ± 0.50	
	6-month	26	6.0 ± 0.42	33	6.2 ± 0.47	0.17
LVESD (cm)	Baseline	33	5.5 ± 0.52	34	5.7 ± 0.56	
	6-month	26	5.2 ± 0.65	34	5.4 ± 0.59	0.091
LVEF (%)	Baseline	34	25 ± 5	36	26 ± 5	
	6-month	28	28 ± 5	34	28 ± 6	0.61
LV mass (g)	Baseline	33	296 ± 59	34	317 ± 59	
	6-month	25	275 ± 63	33	300 ± 56	0.44

Control, standard medical therapy alone; *n*, number of available values; SD, standard deviation.

Table 6 Summary of adverse events

	Alginate-hydrogel (n = 35)		Control (n = 38)		HR (95% CI)	P
	Total no. of events	No. of patients with events (incidence per 100 patient-years at risk)	Total no. of events	No. of patients with events (incidence per 100 patient-years at risk)		
All adverse events	115	31 (489.1)	63	17 (119.1)	3.41 (1.87−6.22)	<0.001
Serious adverse events	33	16 (135.4)	26	10 (63.0)	2.08 (0.94−4.60)	0.063

Control, standard medical therapy alone; *n*, number of patients; HR, hazard ratio; CI, confidence interval. *P*, log-rank *P*-value.

suggestion that this was a result of complications or a complicated post-operative course in general. Excluding all 22 patients who experienced an adverse event during the index hospitalization (within 30 days after surgery) results in a median LOS of 12.5 days, i.e. it did not significantly change overall hospital LOS. Hence, the longer than expected LOS appears to be a reflection of a cautious approach by investigators to discharge patients home following this initial experience with a novel device and procedure.

The 30-day all-cause mortality associated with the implantation of the alginate-hydrogel device was the primary safety endpoint for this study. In total, three deaths occurred during the 30-day period after the surgical procedure to implant the alginate-hydrogel device (8.57% in the mITT population, 95% CI 1.80−23.06%) (*Table 9*). This met the primary safety endpoint for the study, and it is comparable with mortality rates observed in prior reports of surgical device-based therapies for HF. For example, Mann *et al.*[9] reported a 30-day mortality of 7.8% for advanced HF patients receiving the Acorn CorCap device, and Grossi *et al.*[10] reported a 30-day mortality of 8.1% for advanced HF patients receiving the Myocor Coapsys device.

The major surgical complication rate for the alginate-hydrogel device procedure was 25%. Overall, 6-month mortality was higher for patients receiving the alginate-hydrogel device with six deaths compared with three in the Control group. The 30-day MACE rate

during the index hospitalization was 15%. The 6-month MACE rate excluding the index hospitalization was lower for patients receiving alginate-hydrogel and mostly appears to have been attributed to lower rates of hospitalizations due to worsening HF. Conclusions from this information are not possible, as power is limited and none of the differences were significant.

An important consideration for assessing the risks of the alginate-hydrogel therapy will be observations of long-term mortality and longer term clinical benefits from longer follow-up and future studies. These data will provide important context on whether the early risks associated with surgery can be offset by later benefits.

A theoretical concern of intra-myocardial injections/implants is that they could be a basis for sustained ventricular arrhythmias as seen with the prior experience of myoblast therapy. Therefore, the absence of any increase in ventricular arrhythmia or ventricular ectopy in alginate-hydrogel patients is reassuring.

Thus the results of the AUGMENT-HF trial suggest that alginate-hydrogel can be administered safely in patients with advanced HF.

Limitations

A primary limitation of this current study is the lack of blinding for the assignment of patients to surgical device therapy. Endpoints such

Table 7 Major adverse cardiac events excluding index hospitalization

Event	Modified ITT				HR (95% CI)	P-value	ITT				HR (95% CI)	P-value
	Alginate-hydrogel (n = 35)		Control (n = 38)				Alginate-hydrogel (n = 40)		Control (n = 38)			
	Total no. of events	No. of patients with events (incidence per 100 patient-years at risk)	Total no. of events	No. of patients with events (incidence per 100 patient-years at risk)			Total no. of events	No. of patients with events (incidence per 100 patient-years at risk)	Total no. of events	No. of patients with events (incidence per 100 patient-years at risk)		
All-cause death	6	6 (38.4)	3	3 (16.6)	2.32 (0.58–9.26)	0.22	6	6 (37.3)	3	3 (16.6)	2.26 (0.57–9.05)	0.24
Cardiovascular death	5	5 (32.0)	3	3 (16.6)	1.94 (0.46–8.11)	0.36	5	5 (31.1)	3	3 (16.6)	1.89 (0.45–7.93)	0.37
MACE events (excluding index hospitalization)	9	7 (47.2)	22	10 (61.3)	0.78 (0.30–2.04)	0.61	9	7 (45.8)	22	10 (61.3)	0.76 (0.29–2.00)	0.58
All-cause hospitalization	18	10 (76.4)	27	12 (75.9)	1.01 (0.44–2.34)	0.98	18	10 (73.9)	27	12 (75.9)	0.98 (0.42–2.27)	0.96
Heart failure hospitalization	5	4 (26.8)	14	8 (48.4)	0.56 (0.17–1.85)	0.33	5	4 (26.0)	14	8 (48.4)	0.54 (0.16–1.80)	0.31
All-cause hospitalization or CV death	23	13 (99.6)	30	12 (75.9)	1.30 (0.59–2.85)	0.51	23	13 (96.2)	30	12 (75.9)	1.26 (0.57–2.76)	0.56
HF hospitalization or CV death	10	9 (60.7)	17	8 (48.4)	1.25 (0.48–3.25)	0.64	10	9 (58.9)	17	8 (48.4)	1.22 (0.47–3.17)	0.68

Major adverse cardiac event are defined as cardiac death, cardiac arrest, myocardial infarction, sustained ventricular arrhythmias, pulmonary oedema, acute HF, unstable angina, and major bleeding.
P-value, log-rank P-value; MACE, major adverse cardiac events; HF, heart failure; CV, cardiovascular; N, number of patients; HR, hazard ratio; CI, confidence interval.

Table 8 Overall major adverse cardiac events

Event	Modified ITT				ITT			
	Alginate-hydrogel (*n* = 35)		Control (*n* = 38)		Alginate-hydrogel (*n* = 40)		Control (*n* = 38)	
	Total no. of events	No. of patients (%)	Total no. of events	No. of patients (%)	Total no. of events	No. of patients (%)	Total no. of events	No. of patients (%)
Overall MACE	18	11 (31.4%)	22	10 (26.3%)	18	11 (27.5%)	22	10 (26.3%)
MACE during index hospitalization	9	6 (17.0%)		NA	9	6 (15.0%)		NA
Cardiovascular death	2	2 (5.7%)		NA	2	2 (5.0%)		NA
Cardiac arrest	2	2 (5.7%)		NA	2	2 (5.0%)		NA
Worsening HF	1	1 (2.9%)		NA	1	1 (2.5%)		NA
Major bleeding	3	3 (8.6%)		NA	3	3 (7.5%)		NA
Sustained ventricular arrhythmias	1	1 (2.9%)		NA	1	1 (2.5%)		NA

Major adverse cardiac events are defined as cardiac death, cardiac arrest, myocardial infarction, sustained ventricular arrhythmias, pulmonary oedema, acute HF, unstable angina, and major bleeding.
Overall, MACE include all MACE from baseline to 6 months (including index hospitalization).
MACE, major adverse cardiac events; *N*, number of patients.

Table 9 Listing of cause of death

Patient ID	Study group	CEC adjudication		Days post-randomization
RO-48-0063	Alginate-hydrogel	Cardiovascular	Intra-cranial haemorrhage	28
RO-44-0095	Alginate-hydrogel	Cardiovascular	Sudden death witnessed	32
RO-47-0083	Alginate-hydrogel	Cardiovascular	Non-haemorrhagic stroke	33
RO-44-0071	Control	Cardiovascular	Cardiac arrest	38
RO-44-0017	Control	Cardiovascular	Congestive HF/cardiogenic shock	39
RO-44-0019	Alginate-hydrogel	Non-cardiovascular	Infection (including sepsis)	69
NL-32-0026	Alginate-hydrogel	Cardiovascular	Congestive HF/cardiogenic shock	85
RO-44-0069	Alginate-hydrogel	Cardiovascular	Other vascular: 10 days following cardiac transplant	165
IT-21-0035	Control	Cardiovascular	Congestive HF/cardiogenic shock	165

as exercise testing (which depend on patient effort) and subjective endpoints such as NYHA functional class can be subject to bias in a non-blinded trial. We used blinded core laboratory assessments wherever possible to generate valid data as much as possible. Additionally, the limited sample size (35 patients undergoing the surgical device procedure) requires some caution when drawing conclusions and a larger trial experience will be needed to validate the findings.

The mean RERs for the study cohort were <1.05 at all-time points and in both treatment groups. However, the 25th to 75th percentile of RER was 0.95−1.08 and the 25th to 75th percentile were also essentially unchanged across the visits. While an RER >1.05 or 1.10 is often used as a criterion to judge presence of a maximum effort during CPX, prior reports have observed that a very large percentage of chronic HF patients are unable to achieve an RER of >1.00 when performing the CPX test.[28] The consistency of the RER over the course of the study and the duplication of exercise tests at important time points suggest that the changes in peak VO_2 over time were not a result of changes in effort and support the consistency and reproducibility of the test results.

None of the echocardiographic measures in this study reached statistical significance for the group comparisons. This is not surprising given the small size with respect to measures of echocardiography. Additionally, many HF therapies require relatively long time periods to reach a maximal effect or demonstrate reverse re-modelling. It is possible that a longer observation period is needed to realize the full impact of alginate-hydrogel treatment on measures LV remodelling. Future studies need to study cardiac function in more detail.

Table 10 **Listing of causes for non-heart failure hospitalizations**

Patient ID	Study group	Hospitalization	Investigator event term	Fatal outcome	CEC adjudicated
AU-38-0010	Alginate-hydrogel	1	Central chest pain	No	NA
		2	Continuation of atypical centralized chest pain		
AU-38-0070	Alginate-hydrogel	3	Acute injury of chronic renal failure	No	NA
			Worsening bilateral peripheral oedema		
IT-20-0016	Alginate-hydrogel	4	Lobar right pneumonia	No	NA
IT-20-0094	Alginate-hydrogel	5	Erysipelas bilateral lower limbs	No	NA
		6	Worsening HF		
			Septic shock due to legionella pneumonia		
			Acute cholangitis		
IT-20-0109	Alginate-hydrogel	7	Hemisyndrome facio-brachio-crural right	No	NA
		8	Hypertensive crisis associated with pulmonary oedema		
		9	Respiratory infection		
		10	Syndrome of Dressler		
NL-32-0026	Alginate-hydrogel	11	Sepsis	Yes	CV
			Haematoma at location of surgery wound		
			Critical illness polyneuropathy syndrome secondary to sepsis		
RO-44-0019	Alginate-hydrogel	12	Right-sided pneumonia with poliresistant Klebsiella	Yes	Non-CV
RO-44-0069	Alginate-hydrogel	13	Cardiac transplant	Yes	CV
DE-16-0096	Control	14	Worsening of mitral function	No	NA
		15	Symptomatic persistent atrial fibrillation		
IT-18-0057	Control	16	Symptomatic tachycardia	No	NA
IT-49-0048	Control	17	Supraventricular tachycardia provoking two ICD shocks	No	NA
RO-44-0055	Control	18	Syncope	No	NA
RO-44-0071*	Control	19	Worsening of HF	No	NA
RO-47-0054	Control	20	Sustained ventricular tachycardia	No	NA
RO-48-0046	Control	21	Interstitial pneumonia	No	NA
			Planned hospitalization for assessment for cardiac transplantation		
		22	Worsening of HF		
		23	Planned hospitalization for cardiac catheterism		
		24	Junctional rhythm		
		25	Planned hospitalization for investigation for cardiac transplantation		

Table 11 **Assignment of patients by country**

	Informed consent	Screening failure	Randomized (% of randomized)		Surgery (% of randomized to Algisyl-LVR)	
			Control	Alginate-hydrogel	Did not perform surgery	Alginate-hydrogel implanted
All patients	113	35 (31.0%)	38 (48.7%)	40 (51.3%)	5 (12.5%)	35 (87.5%)
Australia	3	1 (33.3%)	0 (0.0%)	2 (100.0%)	0 (0.0%)	2 (100.0%)
Germany	7	4 (57.1%)	2 (66.7%)	1 (33.3%)	1 (100.0%)	0 (0.0%)
Italy	45	21 (46.7%)	10 (41.7%)	14 (58.3%)	2 (14.3%)	12 (85.7%)
The Netherlands	5	3 (60.0%)	1 (50.0%)	1 (50.0%)	0 (0.0%)	1 (100.0%)
Romania	52	5 (9.6%)	25 (53.2%)	22 (46.8%)	2 (9.1%)	20 (90.9%)

Data are number of patients (%).

Conclusion

The AUGMENT-HF trial documents that surgical treatment with alginate-hydrogel was effective in improving exercise capacity and symptoms in patients with advanced chronic HF. The safety profile of this device treatment is acceptable. Further clinical trial experience is needed to validate these promising results.

Appendix 1

Steering committee

Stefan D. Anker (chair), Douglas L. Mann (co-chair), Andrew J.S. Coats, Robert Dowling, and Hani N. Sabbah

Clinical events committee

Nicolas Danchin (Chair), Gerasimos Filippatos, and Jean-Louis Mas

Data safety monitoring committee

Piotr Ponikowski (Chair), Sidney Goldstein, Tim Clayton, and Arjang Ruhparwar

Investigators/centers

The study was performed in centers of 5 countries (*Table 11*).

- Australia: Prof. Tony Dart, Heart Center at the Alfred, Melbourne
- Germany: Prof. Robert Bauernschmitt, Universitätsklinikum Ulm, Ulm; Dr Hakim-Maibodi, Herz- und Diabeteszentrum Nordrhein Westfalen, Bad Oeynhausen; Prof. Klaus Matschke, Herzzentrum Dresden Universitätsklinik, Dresden
- Italy: Dr Ottavio Alfieri, Instituto Scientifico Univ. San Raffaele, Milan; Prof. Antonello Gavazzi, Azienda Ospedaliera Ospedali Riuniti di Bergamo, Bergamo; Prof. Fabio Miraldi, Policlinico Umberto I Rome, Rome; Dr Andrea Mortara, Policlinico di Monza, Monza; Dr Enrico Pusineri, IRCCS Policlinico San Donato, San Donato; Prof. Pirelli Salvatore, Istituti Ospitalieri di Cremona, Cremona; Prof. Maurizio Volterrani, IRCCS San Raffaele, Rome
- The Netherlands: Dr Benno Rensing, St. Antonius Ziekenhuis Nieuwegein, Nieuwegein
- Romania: Prof. Garbiel Cristian, Military Hospital, Bucharest; Dr Dinu Dragomir, Spitalul Clinic De Urgenta MAI, Bucharest; Dr Sorin Stamate, Clinica de Cardiologie Spitalul Clinic Urgenta, Bucharest

Appendix 2

Figure A1

Figure A1 Consort diagram.
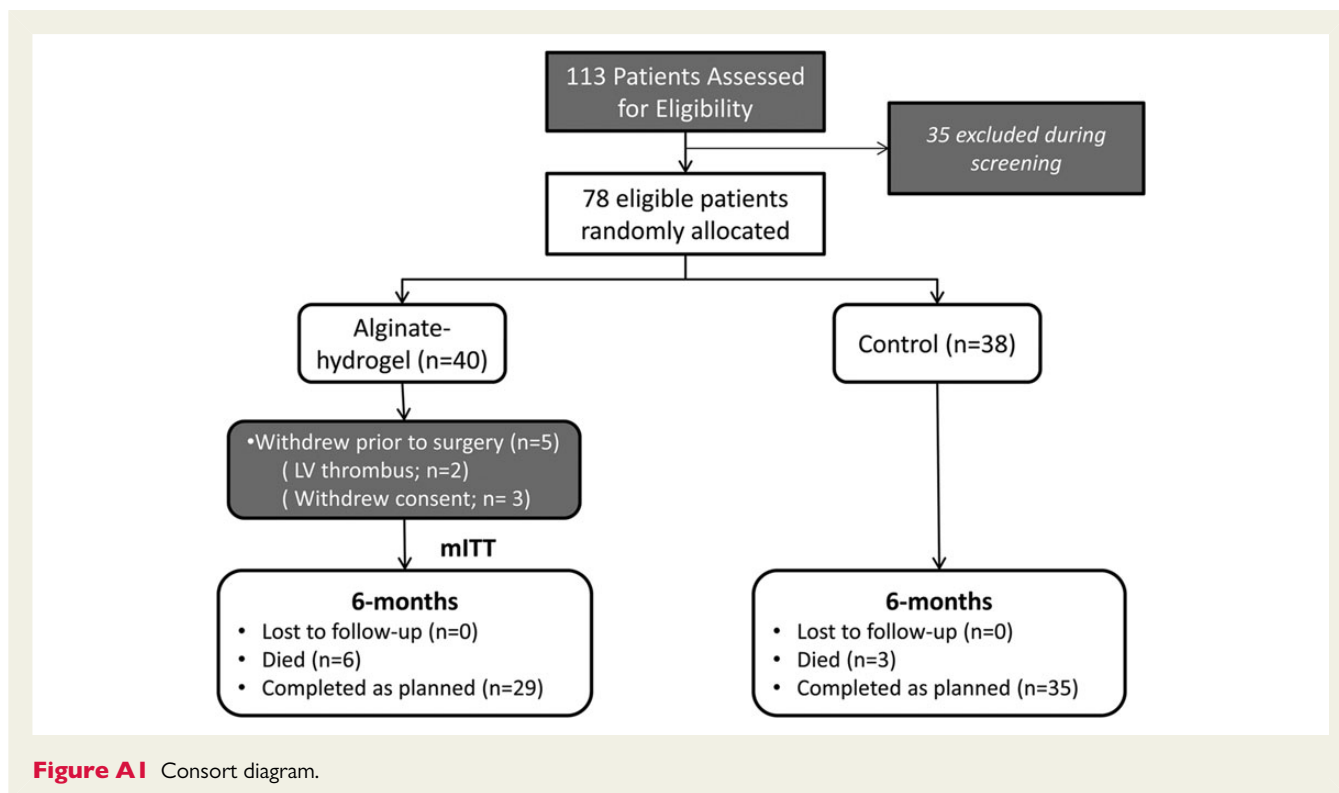
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