

# The need for dedicated advanced heart failure units to optimize heart failure care: impact of optimized advanced heart failure unit care on heart transplant outcome in high-risk patients

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## Abstract

**Aim** With an increasing prevalence of heart failure (HF), more patients with advanced disease have to be treated in cardiology units by sophisticated medical and interventional strategies. We therefore developed a dedicated advanced heart failure unit (AHFU) to target the specific needs of the many patients with advanced HF. We here present our concept and its impact on outcome in high-risk high-urgency (HU) heart transplant candidates.

**Methods and results** The eight-bed unit was established as an extension of the cardiologic intensive care and coronary care units in an intermediate care setting. Each bed was equipped with 24 h haemodynamic, respiratory, and arrhythmia monitoring. The unit is served 24/7 by five residents in cardiology, one staff cardiologist specializing in medical and interventional HF care, and 10 intensive care nurses. The cardiology team is supported by colleagues from cardiac surgery, sports medicine, psychosomatics, and the internal medicine departments. As an example of the intensified care on the AHFU, data from the cohorts of patients undergoing heart transplantation from HU status before (pre-AHFU 2008–11) and after establishment of the AHFU (AHFU 2012–15) were analysed. Interestingly, mortality on HU waiting list and post-heart transplant survival was comparable in both cohorts, despite significant increase in morbidity and co-morbidity as assessed by the Index for Mortality Prediction After Cardiac Transplantation model in the AHFU group.

**Conclusions** Our AHFU provides a unique and novel setting for the integration of modern pharmacological, interventional, surgical, and supportive HF therapy embedded in an academic heart centre. This may be a major step forward in the care of critical patients with advanced HF.

**Keywords** Advanced heart failure; Heart transplantation; Heart failure care

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## Introduction

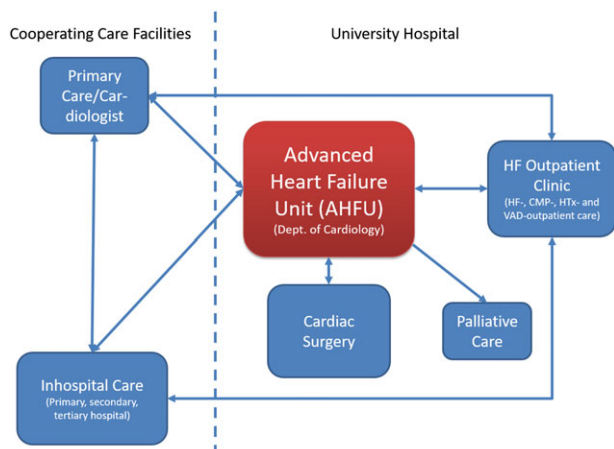
In Western industrialized countries, the prevalence of heart failure (HF) is continuously increasing.<sup>1,2</sup> Recent surveys suggest that ~1–2% of the adult population has HF, and the risk of developing HF for a 40-year-old person during the rest of its life is ~40%. Meanwhile, HF is the most common diagnosis

requiring in-hospital treatment in Germany and other European countries.<sup>3</sup> The reasons for these developments are multifactorial, including an aging population and continuously improving therapeutic options for treatment of acute myocardial infarction or HF with patients surviving acute critical illness. Despite substantial advancements in treatment options, HF remains as a progressive disease with

significant morbidity and mortality.<sup>4</sup> Thus, in clinical care, advanced HF characterized by New York Heart Association (NYHA) III–IV or the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) 1–4 symptoms,<sup>5</sup> episodes of fluid retention, peripheral hypoperfusion, severely reduced cardiac function and exercise capacity, and recurrent hospitalizations demands an increased attention.<sup>2</sup> These patients are at risk for in-hospital death owing to therapy-refractory HF and often require medical or mechanical cardiac inotropic support or heart transplantation.<sup>2</sup> Patients with advanced HF are also characterized by a high prevalence of multiple co-morbidities.<sup>2</sup> HF and co-morbidities are mutually affecting outcome and limit therapeutic options, and thus, treatment becomes increasingly complex. While treatment of acute coronary syndromes was significantly advanced and improved by implementation of chest pain units (CPU) and coronary care units (CCUs),<sup>6,7</sup> no specialized in-hospital care for patients with acute and advanced chronic HF is implemented in cardiologic departments across Europe.

Thus, optimization of in-hospital care of acute, chronic, and advanced HF remains an unmet need. We explored an established dedicated unit with a multidisciplinary team approach to optimize care of patients with acute HF, decompensated chronic HF, and in particular advanced forms of acute and chronic HF. We here present this novel concept of an advanced HF unit (AHFU) embedded in an academic hospital infrastructure and serving as the central co-ordinator for advanced and terminal HF patients in regional and over-regional collaborations (*Figure 1*). In addition, we give an

**Figure 1** Advanced heart failure unit (AHFU) is the central co-ordinator of diagnostic and therapeutic care for advanced and terminal heart failure (HF) patients. The AHFU is embedded in a network with external partners in private practice and cooperating primary, secondary, and tertiary hospitals. Within the University Hospital, a close collaboration with cardiac surgery and our HF outpatient clinic [including HF, cardiomyopathy (CMP), heart transplant (HTx), and ventricular assist device (VAD) outpatient care] was established. In case of terminal HF state without reasonable therapeutic option, palliative care is initiated.



example of our concept of intensified and integrated HF care on our AHFU in a retrospective approach. Therefore, we analysed the data from a cohort of high-risk patients undergoing heart transplantation from high-urgency (HU) status on our AHFU (AHFU cohort, 2012–15) and compared this cohort with a historical control group (pre-AHFU cohort, 2008–11) at our centre.

## Materials and methods

In the Department of Internal Medicine III (Cardiology, Angiology and Pneumology) at the University Hospital Heidelberg, a new intermediate care unit focusing on optimized in-hospital HF care was established in 2012.<sup>8</sup> Patients with acute and advanced chronic HF according to current definitions of the European Society of Cardiology (ESC) were preferably admitted to the AHFU. In daily routine, the AHFU acts as a specialized intermediate care ward for a heterogeneous group of patients with acute HF and patients with worsening of chronic HF. Patient selection criteria are not strictly defined and include (i) 'too sick for a regular ward', (ii) 'potential candidate for heart transplantation or ventricular assist device (VAD)', (iii) patients with unclear destination, and (iv) patients with cardiogenic shock but do not require respiratory support and others. These selection criteria result in a heterogeneous patient population ranging from aged to young patients, patients with a single cardiac disease, and patients with many co-morbidities including acute (or chronic) renal failure and different aetiologies of HF.

We here present the concept of our AHFU and analyse patient characteristics, referral pathways, aetiologies of HF, and treatment strategies for patients treated at the AHFU from 2012 to 2014. In addition, the patient population transplanted from HU status owing to terminal HF (2012–15) was used as an example to demonstrate the concept of intensified HF care on the AHFU cohort and compared with the HU cohort before establishment of the AHFU (2008–11). Patients with, e.g. mechanical circulatory support, were not used for comparison between pre-AHFU and AHFU, because this patient group was very heterogeneous at the AHFU and many patients dependent from short-time or long-time mechanical circulatory support were rather treated at intensive care unit (ICU) or cardiothoracic surgery units. Further, technical improvements and gained experiences may explain improved outcomes in the AHFU period, making mechanical circulatory support a rather inferior measure for structural improvements related to AHFU.

## Concept of AHFU Heidelberg

The concept of the AHFU Heidelberg is based on (i) a specially equipped ward, (ii) a unique team approach, (iii) a diagnostic

approach tailored to HF, and (iv) state-of-the-art HF therapies focusing on each patient's individual needs.

(i) The AHFU is located next to the cardiac ICU and CCU of our department and is equipped with eight treatment units (*Table 1*). Two treatment units are located within one patient room, and each patient room is equipped with a bathroom for convenience. The AHFU is designed as an intermediate care facility. Acute and intensive care options include non-invasive and invasive monitoring, non-invasive ventilation, and percutaneous cardiac support (*Table 1*). The monitors are connected to the wireless network and thus ensure preservation of patient's mobility. Physical training equipment (including several bicycle ergometers and lying bicycle ergometer) allow targeted exercise, when appropriate (*Table 1*).

(ii) Given the predominance of non-surgical treatment options, the AHFU is managed by the department of cardiology. Full expertise in implantation of permanent pacemakers, implantable cardioverter defibrillators (ICDs), and cardiac re-synchronization therapy (CRT) devices is given, and the AHFU is able to initiate and maintain percutaneous cardiac and haemodynamic support including extracorporeal life support (ECLS) therapy. To allow this, the unit is served 24 h a day,

**Table 1** Equipment of the AHFU Heidelberg

AHFU equipment	
Treatment units	8
Monitoring (ECG and automatic blood pressure measurement)	8 1 per treatment unit
Wireless monitoring system	8 1 per treatment unit
Blood gas analysis (including lactate)	Point-of-care test
12-lead ECG	2
Transthoracic echocardiography	365 days/24 h
Transesophageal echocardiography	365 days/24 h
Invasive blood pressure measurement	8 1 per treatment unit
Invasive haemodynamics measurement (via Swan-Ganz catheter)	8 1 per treatment unit
External defibrillator/pacemaker	2
Pacemaker/ICD/CRT interrogation	365 days/24 h
Percutaneous cardiac assist (intra-aortic counterpulsation, Impella, and ECLS)	365 days/24 h
Haemodialysis/ultrafiltration	365 days/24 h
Physical therapy equipment (p.e. bicycle ergometer)	4 1 per 2 treatment units

AHFU, advanced heart failure unit; CRT, cardiac re-synchronization therapy; ECG, electrocardiogram; ECLS, extracorporeal life support; ICD, implantable cardioverter defibrillator.

7 days a week by five residents in cardiology, one staff cardiologist specializing in medical and interventional HF care, and 10 intensive care nurses trained in HF care. In addition, a physiotherapist from the department of physical medicine supports the team to provide physical training beginning with admission to AHFU (*Table 2*). For each patient, 45 min of physiotherapy is integrated in the daily patient routine adapted to the patients' needs and clinical condition. Nevertheless, a close collaboration with cardiac surgery and complementary consultants on a daily basis as needed ensures a comprehensive patient-centred HF care (*Table 3*). Grown-ups with congenital heart disease and HF are treated interdisciplinary together with paediatric cardiology. Nephrology is involved in cardio-renal syndrome and haematology regarding patients with cardiac amyloidosis. In patients with suspected malnutrition, food intake is registered and nutritional medicine involved regarding supplementation. As patients with chronic HF can develop reactive depression, the psychosomatics department is consulted for psychotherapy or initiation of antidepressants. At our weekly heart transplant meeting with cardiac surgery and appropriate consultants, cases are discussed in detail in an interdisciplinary approach.

(iii) The standard diagnostic approach includes patients' basic history, physical examination, 12-lead electrocardiogram, chest X-ray, echocardiography (transthoracic and transoesophageal if necessary), cardiac catheterization (including invasive haemodynamics and endomyocardial biopsy), cardiac magnetic resonance imaging, and genetic testing, when appropriate. Regular measurements of body weight, fluid balances, central venous oxygen saturation, and arterial pressure guide daily therapeutic decisions. If appropriate, each treatment unit allows continuous invasive haemodynamic assessment via Swan-Ganz catheter measurements. A multitude of further diagnostic facilities are provided within the infrastructure of the University Hospital.

(iv) Identifying and treating the cause of HF and understanding haemodynamics and the severity and systemic effects are of utmost importance to our approach. Our therapeutic algorithm covers acute and chronic HF (*Figure 2*).

**Table 2** Human resources at advanced heart failure unit to provide optimal care 24 h/7 days a week

Human resources at AHFU	
Physicians	5 Three-shift operation 365 days/24 h
Nurses	10 Three-shift operation 4 patients : 1 nurse
Physiotherapist	2
Supply-chain assistant	2
Senior physician rounding	Twice daily

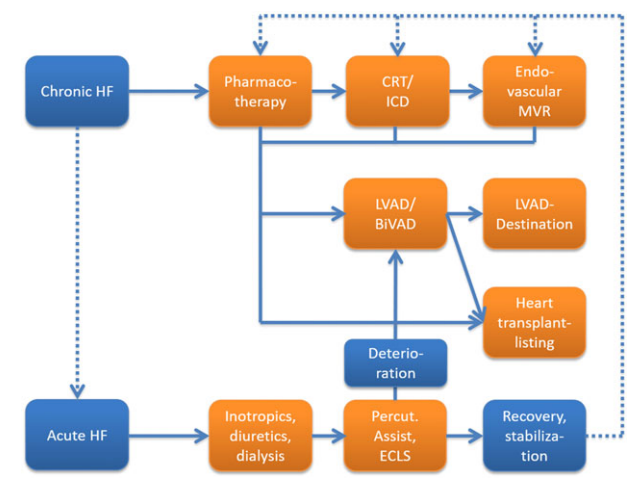
AHFU, advanced heart failure unit.

**Table 3** Structural environment and care facilities in the vicinity of the advanced heart failure unit

AHFU structural environment	
Availability AHFU	365 days/24 h
Chest pain unit	365 days/24 h
Cardiac intensive care unit	365 days/24 h
Clinical chemistry	365 days/24 h emergency value turnaround 30 min
X-ray (chest, abdomen)	365 days/24 h
CT, including cardiac CT	365 days/24 h
Cardiac MRI	Workdays
Genetic testing (for genetic cardiomyopathies)	Workdays
Cardiac catheterization laboratory (for coronary and structural heart disease interventions, myocardial biopsy)	365 days/24 h
Pacemaker operating room	365 days/24 h
Cardiac surgery (VAD and heart transplant service)	365 days/24 h
Consulting services (paediatric cardiology, nephrology, pulmonology, gastroenterology, haematology, nutritional medicine, general and visceral surgery, vascular surgery)	365 days/24 h
Meeting of advanced HF and heart transplant team (cardiology and cardiac surgery and others)	Weekly

AHFU, advanced heart failure unit; CT, computed tomography; HF, heart failure; MRI, magnetic resonance imaging; VAD, ventricular assist device.

**Figure 2** Therapeutic algorithm of the advanced heart failure unit (AHFU) Heidelberg. HF heart failure, CRT cardiac resynchronization therapy, ICD implantable cardioverter defibrillator, LVAD/BIVAD left/biventricular assist device, ICD implantable cardioverter defibrillator, CRT cardiac resynchronization therapy, MVR endovascular mitral valve repair, ECLS extracorporeal life support.



For acute HF conditions, conservative options including intravenous diuretics, inotropes, vasopressors, or vasodilators are used according to ESC guidelines.<sup>2</sup> For HF conditions refractory to conservative treatment, percutaneous cardiac

support options are available 24/7, including intra-aortic balloon pump, TandemHeart (CardiacAssist Inc., Pittsburgh, PA, USA), and a miniaturized ECLS system (Cardiohelp, Maquet, Rastatt, Baden-Württemberg, Germany). For patients with cardio-renal syndrome refractory to medical treatment, ultrafiltration and haemodialysis are offered.

For chronic HF conditions, optimized medical treatment is established according to ESC guidelines.<sup>2</sup> Cardiac resynchronization and implantable defibrillator therapy devices are implanted when appropriate. For severe functional mitral regurgitation in patients with HF and high surgical risk, we offer a minimally invasive endovascular reconstruction of the mitral valve with the MitraClip system.<sup>9,10</sup> Patients with advanced chronic HF refractory to these therapeutic interventions are prepared for heart transplantation or permanent mechanical circulatory support. Both left and biventricular VAD systems are offered in cooperation with our department of cardiac surgery, and a VAD technician is responsible for technical support post-implantation. The systems are used for bridge to transplant and bridge to candidacy or as destination therapy. When appropriate, patients are prepared for heart transplantation. In case the prerequisites for HU status are fulfilled, accepted, and confirmed during the Eurotransplant audit process, the patient is stabilized and optimized in the AHFU until heart transplant.

### AHFU Heidelberg as the central regional and over-regional co-ordinator for advanced and terminal heart failure patients

The AHFU Heidelberg is embedded in a close network, thus centrally co-ordinating care for advanced and terminal HF patients (Figure 1). Physicians in private practice and primary, secondary, and tertiary care hospitals from regional and over-regional distance refer patients. Patients are transferred to the AHFU for further diagnostics and establishment of the therapeutic strategy (Figure 2), which includes pharmacological, interventional, electrophysiological, and surgical aspects. A close collaboration at the Heidelberg Heart Centre within the Department of Cardiology with our interventional HF team and cardiac electrophysiology and with the Department of Cardiac Surgery ensures optimal patient-tailored therapies. Post-stationary care is crucial and ensured by close liaison with our HF outpatient clinics (including HF, cardiomyopathy, heart transplant, and VAD outpatient care) and the cooperation with physicians in private practice and primary, secondary, and tertiary hospitals. In case of terminal HF state without reasonable options, palliative care can be established in cooperation with the palliative care team of our University Hospital. Thus, we have established the AHFU as central regional and over-regional co-ordinator for advanced and terminal HF patients.

## Study population

To give a description of the AHFU patient population, we retrospectively analysed the data from all patients treated at the AHFU from 2012 to 2014 ( $n = 443$ ) by chart review. A main focus in establishing the unit was an optimized pre-transplant care in HU heart transplant candidates. As such, we focused on heart transplant patients, which were transplanted on HU status in the time frame 2008–15 at our centre as an example population. The cohorts of patients undergoing heart transplantation on HU status before (pre-AHFU 2008–11) and after establishment of the AHFU (AHFU 2012–15) were studied and compared. Data acquired from the clinical routine were analysed retrospectively. The original data from the hospital archive were used for the present analysis. The investigation conforms with the principles outlined in the Declaration of Helsinki.<sup>11,12</sup>

## Risk stratification

To characterize both groups—pre-AHFU (2008–11) and AHFU (2012–15)—we applied a risk stratification model for HF and a risk index for heart transplantation. The Seattle Heart Failure Model (SHFM) was used to predict waiting list mortality, and the Index for Mortality Prediction After Cardiac Transplantation (IMPACT) model was employed to predict mortality after heart transplantation. Both models are well established and performed sufficiently in HU heart transplant patients.<sup>13</sup> Additional variables including age, sex, cardiac diagnoses, NYHA class, INTERMACS score,<sup>5</sup> left ventricular ejection fraction, cardiac index, co-morbidity (renal insufficiency defined as glomerular filtration rate  $< 60$  mL/min, haemodialysis treatment, and diabetes mellitus) were assessed. The models and variables were assessed at the time point of first HU application.

## Endpoint

The primary endpoint of this analysis was one year survival post-HU heart transplantation related to pre-heart transplantation risk as assessed by SHFM and IMPACT scores.

## Statistics

Data are expressed as mean  $\pm$  standard error of the mean. As an exception, N-terminal pro-BNP (NT-pro-BNP) is given as median and inter-quartile range [Q1, Q4] owing to its non-normal distribution. For between group comparisons, a Mann–Whitney  $U$ -test was applied. The Kaplan–Meier method was employed for survival analysis, and differences of the two groups were analysed by the log-rank test.

Numbers at risk were compared by  $\chi^2$  test. A  $P$ -value  $< 0.05$  was considered statistically significant. The authors had full access to the data and take responsibility for its integrity.

## Results

### Study cohorts

First, as a description of the AHFU patient population, all patients admitted to the AHFU between March 2012 and December 2014 ( $n = 443$ ) were retrospectively analysed regarding referral pathways, reason for being admitted, aetiology of HF, and treatment strategy (Figure 3). AHFU patients were at mean age of  $58 \pm 0.7$  years, and 77% were male and had an ejection fraction of  $25 \pm 0.8\%$ . Second, in a comparative approach, data from patients undergoing heart transplantation from HU status between January 2008 and February 2011 ( $n = 63$ ; pre-AHFU cohort) and between March 2012 and December 2015 ( $n = 45$ ; AHFU cohort) were analysed. Baseline characteristics of both HU cohorts are summarized in Table 4. Patients in both groups are young for an HF population as there is an age limit for HU heart transplantation listing (65 years) in the Eurotransplant countries. All patients were Caucasian.

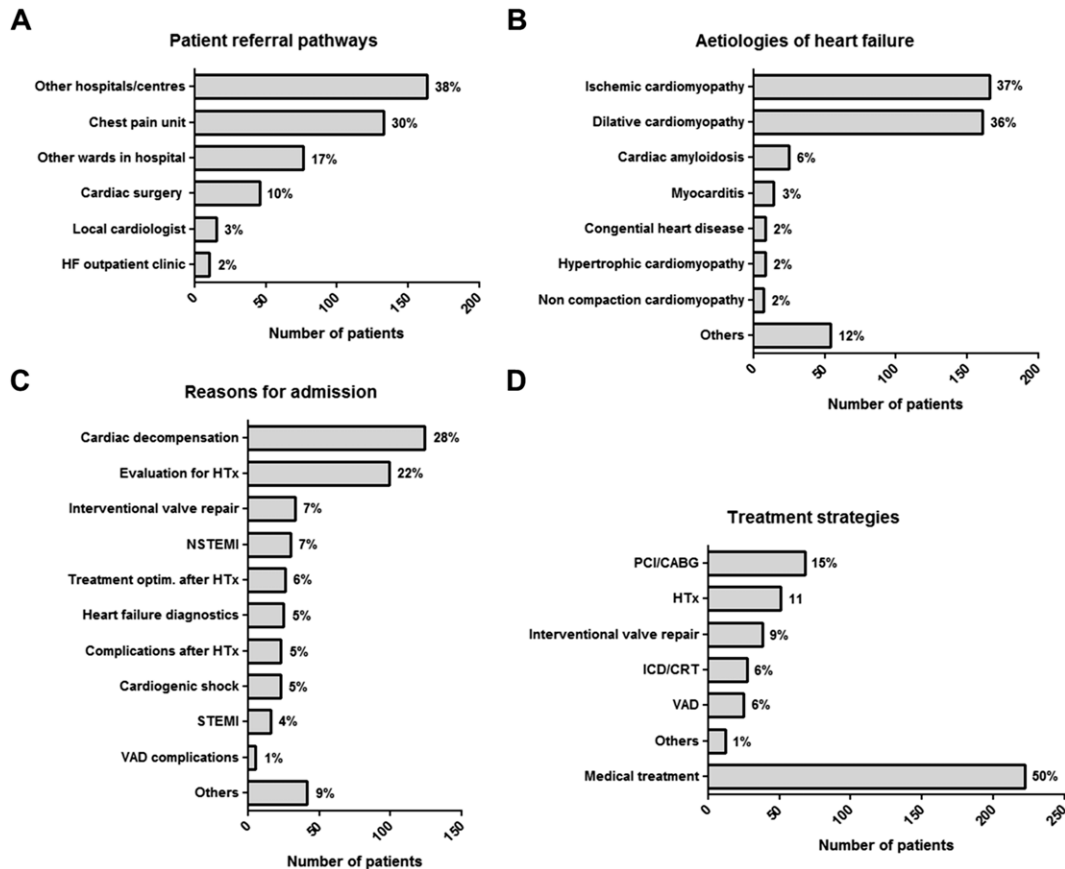
### Heart failure aetiology

Dilated cardiomyopathy and ischaemic heart disease were the most frequent underlying causes of HF in our study groups (Figure 3, Table 4). As a characteristic of our centre, cardiac amyloidosis was present in a relatively frequent number recruited from a large amyloidosis centre integrated at University Hospital Heidelberg.<sup>14</sup> There were significantly more patients with cardiac amyloidosis in the AHFU cohort ( $P = 0.02$ ). Rare causes of HF include congenital heart disease and others.

### Morbidity and co-morbidities in the high-urgency groups

Cardiac function was comparable in both HU groups with regard to left ventricular ejection fraction and cardiac index. The median hospital stay was  $92.9 \pm 10.0$  days for the pre-AHFU cohort and  $97.4 \pm 11.3$  days for the AHFU cohort ( $P = 0.56$ ). The waiting time on HU heart transplantation waiting list was  $63.5 \pm 7.0$  days for the pre-AHFU cohort and  $72.2 \pm 7.1$  days for the AHFU cohort ( $P = 0.2$ ). However, patients in the AHFU group were more symptomatic as shown by significantly higher average NYHA class and lower INTERMACS score than were those in the pre-AHFU cohort

**Figure 3** Characteristics of all patients admitted to the advanced heart failure unit (AHFU) between 2012 and 2014 ( $n = 443$ ). (A) Patient referral pathways. (B) Reason for admission to AHFU. (C) Aetiologies of heart failure. (D) Treatment strategies. HF, heart failure; HTx, heart transplantation; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; VAD, ventricular assist device; PCI, percutaneous coronary intervention; CABG, coronary artery graft bypass; ICD, implantable cardioverter defibrillator; CRT, cardiac re-synchronization therapy.



(Table 4, Figure 4). Significant co-morbidity was present in our AHFU and pre-AHFU cohorts. Renal insufficiency, defined by a glomerular filtration rate of  $<60$  mL/min, calculated by the Modification of Diet in Renal Disease formula, and haemodialysis as well as diabetes were more common in the AHFU cohort compared with the pre-AHFU cohort (Table 4), indicating a more advanced HF in the AHFU cohort. With regard to renal insufficiency, the difference was significant ( $P = 0.048$ ). No significant difference was noted regarding chronic obstructive pulmonary disease, hypertension, diabetes mellitus, and other co-morbidities (Table 4). NT-pro-BNP was slightly higher in the AHFU group albeit not significant. No difference was found between groups regarding ICD and CRT pre-treatment. Medical therapy regarding guideline-recommended HF therapy was not different regarding mineralocorticoid receptor antagonists and beta-blocker treatment (Table 5). Angiotensin-converting enzyme inhibitors and angiotensin receptor 1 blockers were more common in AHFU patients. In the AHFU group, diuretics use was more uncommon,

possibly because of more patients being on dialysis due to renal failure. None of the patients in both groups were on percutaneous or implantable VADs. Nine of 45 in the AHFU group and 14 of 63 in the pre-AHFU group had to be transferred to the ICU owing to respiratory or circulatory failure ( $P = 0.82$ ) but recovered and could be successfully transplanted.

### Risk estimation and survival in the high-urgency groups

With the application of the SHFM model to predict HF mortality, no difference was found in the AHFU cohort compared with the pre-AHFU cohort (Table 4). Interestingly, the well-established and validated IMPACT model to predict mortality after heart transplantation showed a significantly higher risk in the AHFU cohort vs. the pre-AHFU cohort ( $10.8 \pm 1.3$  vs.  $4.8 \pm 1.4$  IMPACT points,  $P < 0.001$ ) (Figure 4).

**Table 4** Patient characteristics of the advanced heart failure unit and the respective control group

	Pre-AHFU (2008–11)	AHFU (2012–15)	P-value
Age	51.9 ± 1.4	53.5 ± 1.4	0.67
Sex			
Male	48 (76%)	34 (76%)	0.94
Female	15 (24%)	11 (24%)	
Diagnosis			
DCMP	31 (49%)	21 (57%)	0.79
ICMP	23 (37%)	11 (24%)	0.18
Amyloidosis	4 (6%)	10 (22%)	0.02
HCM	3 (5%)	0 (0%)	0.14
Other	2 (3%)	3 (7%)	0.73
LV-EF (%)	18.4 ± 0.8	20.3 ± 1.6	0.96
Cardiac index (L/min/m <sup>2</sup> )	1.7 ± 0.04	1.8 ± 0.06	0.02
NYHA class	3.1 ± 0.05	3.3 ± 0.08	0.04
Sinus rhythm	32/63 (51%)	25/45 (55%)	0.58
SHFM			
1 year	70.7 ± 3.6	69.6 ± 3.6	0.32
5 year	36.5 ± 3.8	30.4 ± 3.7	0.32
IMPACT score	4.8 ± 1.4	10.8 ± 1.3	<0.001
INTERMACS level	3.4 ± 0.1	3.2 ± 0.1	0.047
Renal insufficiency	19/63 (30%)	22/45 (49%)	0.048
BUN (mg/dL)	64.71 ± 4.341	60.83 ± 3.323	0.36
Dialysis	5/63 (8%)	15/45 (33%)	<0.001
Diabetes mellitus	10/63 (16%)	10/45 (22%)	0.40
COPD	9/63 (14%)	5/45 (9%)	0.63
Cerebrovascular disease	2/63 (3%)	6/45 (13%)	0.06
Peripheral artery disease	4/63 (6%)	3/45 (7%)	1.00
Hypertension	40/63 (63%)	32/45 (71%)	0.41
NT-pro-BNP (ng/L)	6453 [3562, 12 510]	9064 [3868, 15 286]	0.12
ICD	43/63 (68%)	31/45 (69%)	0.94
CRT	26/63 (41%)	16/45 (36%)	0.55

AHFU, advanced heart failure unit; BUN, bundle urea nitrogen; COPD, chronic obstructive pulmonary disease; CRT, cardiac re-synchronization therapy; DCMP, dilative cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; ICMP, ischaemic cardiomyopathy; IMPACT, Index for Mortality Prediction After Cardiac Transplantation; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LV-EF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-BNP; NYHA, New York Heart Association class; SHFM, Seattle Heart Failure Model 1 and 5 year survival. Mean ± standard error of the mean, median, and [Q1, Q4] or absolute numbers and %. Mann–Whitney test.

**Table 5** Medical treatment for the pre-advanced heart failure unit and the advanced heart failure unit group

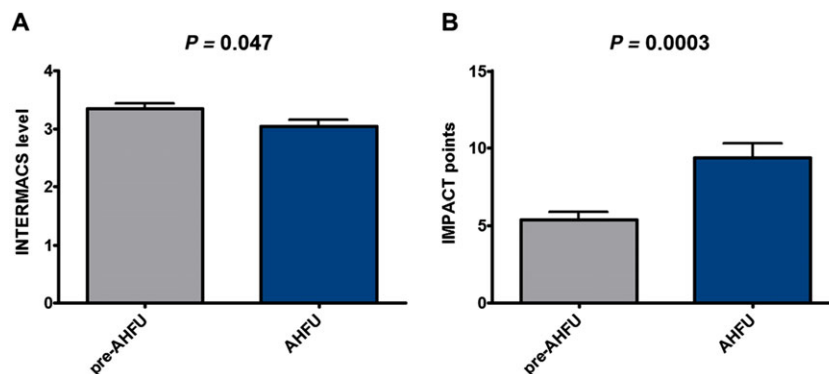
	Pre-AHFU (2008–11)	AHFU (2012–15)	P-value
Beta-blocker	38/63 (60%)	28/45 (62%)	0.20
ACE blocker/AT1-receptor antagonists	36/63 (57%)	37/45 (82%)	0.007
MRA	15/63 (24%)	9/45 (20%)	0.81
Diuretics (HCT, furosemide, torasemide)	56/63 (90%)	33/45 (73%)	0.044

AHFU, advanced heart failure unit; ACE, angiotensin-converting enzyme; AT1, angiotensin 1; HCT, hydrochlorothiazide; MRA, mineralocorticoid receptor antagonist. Absolute numbers and %. Mann–Whitney test.

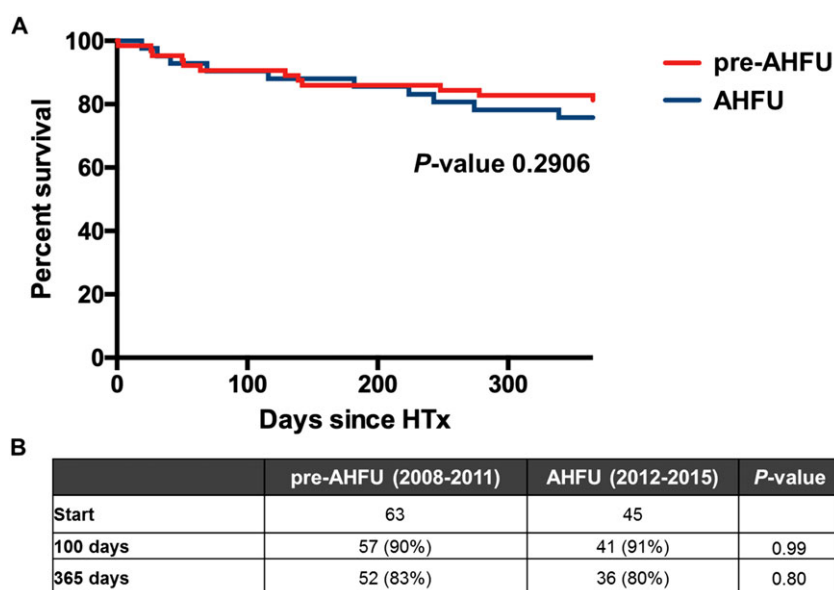
We found a significantly higher risk for post-heart transplantation mortality at time of first HU application in the AHFU cohort vs. the pre-AHFU cohort (*Table 4, Figure 4*). Interestingly, survival was comparable in both cohorts despite significantly higher estimated risk in the AHFU cohort vs. the pre-AHFU cohort (*Figure 5*). Thus, an intensified care entirely tailored towards advanced HF results in comparable outcomes in a population with growing risk. This was also the case for patients prior heart transplantation: When we compared mortality of HU transplant candidates on the HU transplant list between pre-AHFU and AHFU, 24 of 71 patients died 2008–11 (pre-AHFU; 34%), whereas 24 of 66 (36%) patients died 2012–15 (AHFU; *P* = 0.85).

## Discussion

To our best knowledge, we here describe for the first time a novel concept of a multidisciplinary and comprehensive AHFU embedded in an academic heart centre and aimed at integration of guideline-recommended pharmacological therapies and use of devices and monitoring to optimize

**Figure 4** INTERMACS and IMPACT scores in advanced heart failure unit (AHFU) patients undergoing high-urgency heart transplantation. (A) INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) score. (B) IMPACT (Index for Mortality Prediction After Cardiac Transplantation) score. Mean ± standard error of the mean. Mann–Whitney test.

**Figure 5** Survival after high-urgency heart transplantation. (A) Survival and (B) numbers at risk, after high-urgency heart transplantation for the advanced heart failure unit (AHFU) group (2012–15) and the pre-AHFU group (2008–11). Log-rank test (A).  $\chi^2$  test (B). HTx heart transplantation.



in-hospital care for patients with advanced HF. We feel that our AHFU was highly accepted by local partners as well as by other cardiology departments in regional and over-regional distance, which may be reflected by more advanced HF patients in the AHFU cohort that were not only recruited by our own hospital but also transferred from other clinics. Our example cohort of HU heart transplant patients revealed that despite higher risk due to increased morbidity and co-morbidities in the AHFU cohort (2012–15) vs. the pre-AHFU cohort (2008–12), comparable survival until transplantation from HU status and comparable outcomes after heart transplantation were achieved most likely owing to intensified AHFU HF care.

### Advanced heart failure unit in light of status quo of clinical cardiac care

Optimization of in-hospital HF care is an unmet need in Germany and other European countries.<sup>2</sup> Over the last 15 years, specialized clinical cardiac care units as CPUs, CCUs, and cardiac ICUs have been established in many centres. Advanced HF mortality and co-morbidities complicate therapeutic options. Thus, an HF patient needs a specialized approach by an experienced team, which is not covered by existing cardiac care facilities. The AHFU is entirely focused on optimized in-hospital care of advanced chronic HF. The diagnostic and therapeutic algorithm is tailored towards advanced HF patients, as well as staffing and equipment. An AHFU should therefore be complementing

existing cardiac care facilities. Integration into the structural environment and care facilities surrounding the AHFU is critical for success, as rapid transfer to AHFU and potential referral to cooperating facilities (cardiac surgery) will ensure optimal care. Indeed, personnel and structural changes implemented in our AHFU impose increasing costs. However, HU heart transplant candidates comprise a very sick population, which needs an optimized setting. We have established the AHFU aimed at optimal care for this particular population.

### Advanced heart failure unit in light of organ donor shortage

To quantify potential effects caused by improved patient care on AHFU, we aimed to find a homogenous patient population treated at our AHFU for a comparison between pre-AHFU and AHFU periods. We decided to measure outcomes in HU heart transplantation candidates, as the majority of these patients were treated at our AHFU, in contrast to, e.g. patients with mechanical circulatory support, who are often treated in ICU or cardiothoracic surgery units. Moreover, the outcome in latter patients may be rather determined by technical and surgical advances and gained experience with this rapidly developing technology in the last decade. However, cardiac transplantation remains the therapy of choice for many patients with advanced HF who are refractory to other therapeutic approaches.<sup>2</sup> International Society for Heart and Lung Transplantation (ISHLT) data indicate an international one year survival approximating 87% ([www.isHLT.org](http://www.isHLT.org)). The



situation in Eurotransplant and especially in Germany is different owing to the special transplantation tiers including HU heart transplantation, derived by urgency and not transplant success. As such, the results in Germany are worse than the ISHLT data, as focusing solely on urgency indicates higher morbidity causing higher mortality. A continuous decrease in post-mortal organ donors and a simultaneously rising number of patients awaiting heart transplantation further challenge advanced HF care in Germany and the other Eurotransplant countries.<sup>15</sup> Currently, patients listed on HU status predominantly receive heart transplants.<sup>15</sup> Usually, patients on HU status are inotrope dependent, requiring intermediate care accommodation. According to Mancini *et al.*, this patient population with an INTERMACS score of 3 or below has an exceptionally high mortality,<sup>16</sup> and thus non-invasive and invasive monitoring and therapeutic strategies of our AHFU are focused on optimized preparation of these patients for heart transplantation, including continuous provision of mechanical support options in case of deterioration. Advanced disease with significant morbidity and co-morbidity was seen in both cohorts. SHFM was not different between groups. However, SHFM was not established and validated in an advanced, end-stage HF population, and its performance in these HU heart transplant candidates is poor with a C-value of 0.63 as published by Smits *et al.*<sup>13</sup> With respect to INTERMACS level, there was a small but significant difference, and INTERMACS level was lower in the AHFU era. The AHFU cohort with an average IMPACT score of  $10.8 \pm 1.3$  shows an exceptionally increased risk and higher expected mortality. For comparison, the average IMPACT score in the INTERMACS registry before VAD implantation was  $5.1 \pm 3.6$ .<sup>17</sup> Thus, both cohorts presented in our study comprise terminal HF patients at highest risk in need of intensified care. The increase in IMPACT score in the AHFU cohort compared with the pre-AHFU cohort is probably due to continuously increasing waiting times on the normal heart transplant waiting list and may also be due to a concentration of more severe, affected patients from a much larger radius. Overall, a comparable mortality in both groups despite higher risk in the AHFU cohort is noteworthy, albeit we emphasize that outcome of HU heart transplanted patients is potentially

not the optimal measure. Although this comparison has many limitations (small number of patients, retrospective analysis, single centre), and other factors may account for these observations independent from AHFU, e.g. medical progress in general or improvements in post-operative care, our concept may stimulate others to further develop structural organizations and specialized care tailored for patients with advanced HF.

## Conclusions

In Western industrialized countries, the prevalence of HF and resulting HF hospitalizations are continuously increasing. Specialized in-hospital treatment units for advanced chronic HF remain an unmet need. We established an AHFU entirely focused on patient-centred in-hospital HF care. Our AHFU concept includes a dedicated unit, an optimized diagnostic approach, and a therapeutic algorithm tailored to HF in combination with a team led by cardiologists and cooperating with complimentary consultants entirely dedicated to HF and embedded in an academic heart centre. We here report our first experience during the pilot years, which could inspire other HF centres to follow our innovative approach aimed at optimized in-hospital care for patients with advanced chronic HF.

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## Conflict of interest

None declared.

## References

- Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CSP, Sato N, Shah AN, Gheorghiu M. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014; **63**: 1123–1133.
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. 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 Heart J* 2016; **37**: 2129–2200.
- Störk S, Handrock R, Jacob J, Walker J, Calado F, Lahoz R, Hupfer S, Klebs S. Epidemiology of heart failure in Germany: a retrospective database

- study. *Clin Res Cardiol* 2017; **106**: 913–922.
4. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics—2017 update: a report from the American Heart Association. *Circulation* 2017; **135**: e146–e603.
  5. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, Miller MA, Baldwin JT, Young JB. Seventh INTERMACS annual report: 15,000 patients and counting. *J Heart Lung Transplant* 2015; **34**: 1495–1504.
  6. Post F, Giannitsis E, Riemer T, Maier LS, Schmitt C, Schumacher B, Heusch G, Mudra H, Voigtländer T, Erbel R, Darius H, Katus H, Hamm C, Senges J, Gori T, Münzel T. Pre- and early in-hospital procedures in patients with acute coronary syndromes: first results of the “German Chest Pain Unit Registry”. *Clin Res Cardiol* 2012; **101**: 983–991.
  7. Julian DG. The evolution of the coronary care unit. *Cardiovasc Res* 2001; **51**: 621–624.
  8. Tschierschke R, Katus HA, Raake PWJ. First “Advanced Heart Failure Unit” at the Heart Centre of the University Hospital Heidelberg. *Dtsch Med Wochenschr* 2013; **138**: 603–607.
  9. Pleger ST, Schulz-Schönhagen M, Geis N, Mereles D, Chorianopoulos E, Antaredja M, Lewening M, Katus HA, Bekerredjian R. One year clinical efficacy and reverse cardiac remodelling in patients with severe mitral regurgitation and reduced ejection fraction after MitraClip implantation. *Eur J Heart Fail* 2013; **15**: 919–927.
  10. Geis N, Raake P, Mereles D, Chorianopoulos E, Szabo G, Katus HA, Bekerredjian R, Pleger ST. Percutaneous repair of severe mitral valve regurgitation secondary to chordae rupture in octogenarians using MitraClip. *J Interv Cardiol* 2017; **30**: 2013.
  11. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; **310**: 2191–2194.
  12. Declaration of Helsinki. Recommendations guiding doctors in clinical research. Adopted by the World Medical Association in 1964. *Wis Med J* 1967; **66**: 25–26.
  13. Smits JM, de Vries E, De Pauw M, Zuckermann A, Rahmel A, Meiser B, Laufer G, Reichenspurner H, Strueber M. Is it time for a cardiac allocation score? First results from the Eurotransplant pilot study on a survival benefit-based heart allocation. *J Heart Lung Transplant* 2013; **32**: 873–880.
  14. Kristen AV, Kreusser MM, Blum P, Schonland SO, Frankenstein L, Dösch AO, Knop B, Helmschrott M, Schmack B, Ruhparwar A, Hegenbart U, Katus HA, Raake PWJ. Improved outcomes after heart transplantation for cardiac amyloidosis in the modern era. *J Heart Lung Transplant* 2018; **37**: 611–618.
  15. Smits JM. Actual situation in Eurotransplant regarding high urgent heart transplantation. *Eur J Cardiothorac Surg* 2012 Oct; **42**: 609–611.
  16. Mancini D, Lietz K. Selection of cardiac transplantation candidates in 2010. *Circulation* 2010; **122**: 173–183.
  17. Kilic A, Allen JG, Arnaoutakis GJ, George TJ, Cameron DE, Vricella LA, Weiss ES. Adult-derived Index for Mortality Prediction After Cardiac Transplantation (IMPACT) risk score predicts short-term mortality after pediatric heart transplantation. *Ann Thorac Surg* 2012; **93**: 1228–1234, discussion 1234–1235.