Acute heart failure (AHF) is a life-threatening emergency, which largely profits from early diagnosis and treatment. The prevalence of AHF is difficult to assess, estimates range between 1 and 12% in the general population. Despite recent therapeutic advances, in-hospital mortality is high with estimates varying from 4 and 18% in different registries. Due to large differences in AHF definitions and selection criteria AHF populations vary in their characteristics and outcomes. This is especially true for randomized clinical trials and the external validity of some of these trials is questionable. Additionally, the timing of data collection and/or initiation of new therapies vary with the setting of trials. The aim of this article is to call attention to the difference in AHF populations and to emphasize the need for research to clearly define these populations.

AHF populations from registries and clinical trials are the basis for evidence-based management strategies. It is important that these populations represent the patients in whom these strategies will be applied in routine care.
Facts and numbers

Numbers on acute heart failure

It is difficult to assess the numbers on the prevalence of acute heart failure. ICD-10 coding for heart failure distinguishes between different types of heart failure and the severity of symptoms, but a clear assignment of AHF is difficult. Big data analyses often select patients based on a maximum of three digits of the ICD-code in order to not create too many small subgroups, even though coding of all digits is mandatory in German hospitals. For the emergency department, hospitalization for heart failure is usually equalized as AHF, and I50 is the diagnosis which is chosen to define AHF.

Studies on AHF prevalence use different sources for their estimation, as outlined in a publication on the epidemiology of AHF by Rogers. These studies include patient-based assessment (self-report) and routine data analyses (first hospitalization for heart failure, hospital discharge or death certificate with ICD code for HF, hospital discharge diagnosis, and administrative databases, e.g. Medicare). In other studies, defined criteria are applied to count patients with heart failure, e.g. the Framingham Congestive Heart Failure Criteria or the Boston criteria for heart failure. These criteria require prospective patient enrolment or a thorough analysis of well-documented routine data. From all these studies, Roger summarizes an overall prevalence of HF between 1 and 12% in the United States and Europe. The lifetime risk to developing the disease is described as ranging between 20 and 33%. Importantly, the prevalence of heart failure dramatically increases with age. The ESC guidelines refer to a study by Mosterd et al., estimating an overall prevalence in the population of 1–2% and of >10% in the population of persons of and above the age of 70 years. None of these publications provides specific numbers for acute heart failure, indicating the difficulty to group patients into a defined AHF-cohort.

AHF in the emergency department

Acute heart failure is a serious and life-threatening condition, and a large proportion of patients are admitted either directly to an intensive care unit or to an emergency department. In a recent single-day snapshot survey of all unplanned hospitalizations due to AHF in 170 French hospitals, 64% of the patients were admitted via an emergency department. In ADHERE, a large US-based registry on AHF patients, 78% of patients were admitted via the ED.

Presentation of AHF in the emergency department can be challenging and atypical. In the CHARITEM study, which analysed routine hospital data from all patients in internal medicine who presented to one of two German tertiary care emergency departments (n = 34,333), the relationship between chief complaint and underlying main diagnosis was assessed. To evaluate the characteristics of patients with heart failure in the emergency department, we analysed data from all inpatients with a main hospital diagnosis heart failure (ICD-10 code I50, n = 370). We assumed that patients present to the emergency department with an emergency or, at least, with an acute condition, and that the probability of AHF in these patients is high. Doing this, we might have missed patients for whom other codes were used, e.g. in the context of cardiomyopathies as well as patients in whom HF was not coded as the main diagnosis. On the other hand, we might have included patients who presented with a different acute condition, but their HF was coded as the main hospital diagnosis because it became an issue during the further hospital stay.

The most frequent chief complaint in inpatients with the main hospital diagnosis of heart failure in our cohort was acute dyspnoea with 65.1%. Another 9.7% of the patients with HF presented with a chief complaint of chest pain. Interestingly, almost one quarter of patients (23.1%) did not have either of these two complaints, but presented with unspecific symptoms. On the other hand, of the hospitalized patients in CHARITEM with dyspnoea (n = 1497), only a moderate proportion of patients had an underlying diagnosis of HF; the top five main hospital diagnoses were chronic obstructive pulmonary disease (16.5%), heart failure (16.1%), pneumonia (5.5%), acute myocardial infarction (5.3%), and atrial fibrillation (4.9%). Table 1 shows the unpublished characteristics of patients with heart failure analysed from the CHARITEM data as compared with all inpatients enrolled in CHARITEM. The median age in the hospitalized patients with HF in the emergency department was 71 years. Women, who represented 41% of the patients with HF, were almost 10 years older than the men (median age: 68 years). The patients with HF had a higher breathing rate, lower oxygen saturation, and higher creatinine values compared with all inpatients, and they had a longer length of hospital stay. The inhospital mortality in the HF group was 8.4%. The median GFR in patients with heart failure was 51 mL/min (34/72) per 1.73 m².

Table 2 shows the full 5-digit ICD-10 codes of the CHARITEM patients with HF. From this coding, especially in the setting of an emergency department, it is difficult to define patients with clear AHF, especially, as symptoms at presentation to the ED are relevant. Therefore, any HF diagnosis in combination with the hospitalization via an ED is counted as AHF.

CHARITEM was approved by the ethics committee of the Charité — Universitätsmedizin Berlin. The study complies with the Declaration of Helsinki.

Acute heart failure in registries

A large number of AHF registries have been set up worldwide. Pang et al. recently published an educational consensus paper for which an international group of experts had convened to
Table 1 Patient characteristics in the emergency department of hospitalized patients with heart failure (ICD-10 codes I50) from the CHARITEM trial

| Variable                          | All inpatients (n = 13,536) | Inpatients with HF (ICD-10 code I50) (n = 370) | Women with HF (n = 151) | Men with HF (n = 218) |
|-----------------------------------|-----------------------------|-----------------------------------------------|-------------------------|-----------------------|
| Age*                             | 67 (53/75)                  | 71 (65/80)                                    | 77 (69/85)              | 68 (62/76)            |
| Female                            | 45.9%                       | 40.8%                                         | —                       | —                     |
| Chief complaint at presentation   |                             |                                               |                         |                       |
| Dyspnoea                          | 11.1%                       | 65.1%                                         | 64.2%                   | 66.1%                 |
| Chest pain                        | 13.9%                       | 9.7%                                          | 6.6%                    | 11.5%                 |
| Abdominal pain                    | 8.9%                        | 1.4%                                          | 2.0%                    | 0.9%                  |
| Headache                          | 2.3%                        | —                                             | —                       | —                     |
| None of these                     | 63.8%                       | 23.8%                                         | 27.2%                   | 21.5%                 |
| Respiratory rate                  | 16 (15/18)/min              | 18 (16/22)/min                                | 19 (16/23)/min          | 18 (15/21)/min        |
| Oxygen saturation*                | 97 (95/98)%                 | 94 (90/97)%                                   | 94 (89/97)%             | 95 (91/97)%           |
| Creatinine (mg/dL)*               | 0.95 (0.8/1.2)              | 1.29 (1.0/1.7)                                | 1.3 (1.0/1.8)           | 1.3 (1.0/1.7)         |
| Length of hospital stay*          | 5 (3/9) days                | 7 (4/13)                                      | 8 (4/13)                | 7 (4/14)              |
| ICU stay                          | 18.2%                       | 30.8%                                         | 31.8%                   | 30.2%                 |
| Mortality                         | 4.7%                        | 8.4%                                          | 9.9%                    | 7.3%                  |

*Median (interquartile range).

Table 2 5-digit ICD-10 codes for the patients in CHARITEM

| ICD-10 code | Text                                      | Number of patients with HF in CHARITEM |
|-------------|-------------------------------------------|----------------------------------------|
| I00.00      | Primary right ventricular heart failure   | 2.2% (n = 8)                           |
| I00.01      | Secondary right ventricular heart failure | 21.6% (n = 80)                         |
| I00.12      | Left ventricular heart failure with symptoms at moderate exercise | 3.5% (n = 13) |
| I00.13      | Left ventricular heart failure with symptoms at mild exercise | 19.7% (n = 73) |
| I00.14      | Left ventricular heart failure at rest    | 42.2% (n = 156)                        |
| I00.19      | Left ventricular heart failure, not specified | 2.2% (n = 8) |
| I00.9       | Heart failure, not specified              | 8.6% (n = 32)                          |
| Total       |                                           | n = 370                                |

Table 3 Inclusion criteria of exemplary AHF registries based in the USA, Europe, and Japan

| Registry | Origin | Definition of AHF cited from the publication or the study registry |
|----------|--------|---------------------------------------------------------------|
| ADHERE6,9 USA | Inclusion criteria: | Age greater than or equal to 18 years at the time of admission to the hospital |
| OPTIMIZE-HF10 USA | Inclusion criteria: | Hospitalized for episode of worsening heart failure as primary cause of admission or significant heart failure symptoms that develop during the hospitalization when the initial reason for admission was not heart failure |
| ATTEND11 Japan | Inclusion criteria: | Inpatients with AHFS who met the modified Framingham criteria, which only includes variables estimated at admission (….) are eligible for the study |
| EHFS II12 30 European countries | Inclusion criteria: | EHFS II recruited patients admitted to the hospital (emergency area, internal medicine/cardiology wards, CCU, or ICU) with dyspnoea and verification of HF (new-onset AHF or ADCHF) based on: Symptoms (dyspnoea) and signs (i.e. rales, hypotenion, hypoperfusion, right ventricular HF) of HF and lung congestion on chest X-ray |
| ESC-HF pilot13 12 European countries | Inclusion criteria: | The following patients were entered in the survey: All outpatients with chronic HF diagnosed according to the clinical judgement of the responsible cardiologist at the participating centres Patients admitted to hospital for acute HF, for whom an intravenous therapy (inotropes, vasodilators, or diuretics) was needed All patients had to be aged over 18 years |

AHF, acute heart failure; LVEF, left ventricular ejection fraction; AFHS, acute heart failure syndrome; CCU, coronary care unit; ICU, intensive care unit; ADCHF, acutely decompensated congestive heart failure.
provide guidance for AHF care. The authors analyse a large set of AHF registries with respect to origin, setting, patient characteristics, treatment, and outcome. The registries use very different criteria to define acute heart failure as outlined in Table 3.

Due to the variety in settings and inclusion criteria, patient characteristics vary between the registries. The mean age of patients ranges between 69 and 79 years, whilst the proportion of women ranges between 37 and 62%. Inhospital mortality also varies widely with proportions between 3.8 and 17.8%. In summary, AHF cohorts in international registries are extremely varied and do not describe comparable patient groups, owing not only to the different healthcare systems, but also to different patient selection based on different definitions of AHF.

Acute heart failure in clinical studies

Clinical trials have the same problem to apply standard criteria for the definition of AHF. Platz et al. were recently able to show that trials use inconsistent criteria for the definition of pulmonary oedema, which is one of the key findings in AHF. The composition of representative AHF cohorts is further hampered by the inclusion and exclusion criteria, which are not only applied to select a uniform cohort, but also to secure patient safety and feasibility of the trial. The differences in enrolment criteria and timing again, results in differences in the study populations, as shown in Table 4.

As a result of the enrolment criteria, only small subsamples of the large population of patients with AHF are eligible to participate in clinical trials. Wang et al. tried to identify potentially eligible patients for a large AHF RCT, Relax-AHF, in the ADHERE registry. They found that only around 2 in 10 patients fulfilled the inclusion and exclusion criteria.

Figure 1 shows the result of a screening effort to find eligible patients for a large, international multicentre RCT on patients with AHF, in which our emergency departments participated. Only 3% of all patients who were screened for eligibility were enrolled.

So far, the issue of the external validity of clinical trials is not well addressed in publications and guidelines. Calls for specific ‘To whom this research applies’ boxes as suggested by Rothwell, indicating which patients are likely to profit from evidence-based therapies, are mainly unheard.

Acute heart failure precipitants and infection

Many patients with acute heart failure present with specific precipitants, which include ACS, arrhythmias, and infection. Typical cases with precipitants have been published online (http://www.eusem.org/onlinecontent/ and http://www.escardio.org/The-ESC/Communities/Acute-Cardiovascular-Care-Association-%28ACCA%29/Education-and-research/patients-cases) in addition to a consensus paper.

| Table 4: Basic patients and trial characteristics for selected multicentre, randomized trials in patients with AHF compared with secondary hospital data in CHARITEM. Numbers are given for the intervention group only |
|----------------|----------------|----------------|----------------|
| RELAX-AHF15    | PRONTO16       | ASTRONAUT17    | CHARITEM7      |
| Age in years (mean/SD) | 71.6 (14.9) | 68.7 (12.4) | 64.2 (12.4) | 71.1 (12.9) |
| Men % | 64% | 46% | 46% | 59% |
| GR (mL/min per 1.73 m²) | 53.7 (13.1) | — | 57.8 (14.3) | 67.3 (13.1) |
| Time until randomization (h) | 7.8 (4.6) h | 3.2 (1.9) h | 1 | — |
| Inclusion criteria as outlined in the method section | All patients presenting to one of two tertiary care EDs who were hospitalized and had a main hospital diagnosis of heart failure (ICD-10 code I50) | All patients presenting to one of two tertiary care EDs who were hospitalized and had a main hospital diagnosis of heart failure (ICD-10 code I50) | All patients presenting to one of two tertiary care EDs who were hospitalized and had a main hospital diagnosis of heart failure (ICD-10 code I50) |

Typical cases with precipitants have been published online (http://www.eusem.org/onlinecontent/ and http://www.escardio.org/The-ESC/Communities/Acute-Cardiovascular-Care-Association-%28ACCA%29/Education-and-research/patients-cases) in addition to a consensus paper.
Decompensation and AHF, secondary to tachycardia or myocardial infarction, are mostly regarded to be straightforward, and treatment of the underlying disease is clear. Infection, specifically of the lower respiratory tract, may not be as obvious as other precipitants and are a challenge for the primary treatment, as patients with pneumonia will profit from very early antibiotic therapy and volume therapy rather than from decongestion and diuretic medication. Therefore, a prospective, international study (IMPACT: ClinicalTrials.gov, NCT02392689) randomizing patients who present acutely with proANP levels above 300 (or BNP > 350 or NT-proBNP > 1800) to be diagnosed with additional procalcitonin vs. the clinical standard including WBC and CRP is on its way.

Future challenges

We need to rethink the research on patients with acute heart failure. The majority of studies on acute heart failure are a domain of cardiologists. These studies are designed, planned, and conducted by cardiologists on cardiology wards, and presented at cardiology congresses.

The actual medical care reality is different. The majority of patients with AHF are admitted via emergency departments. Patient outcome have been shown to improve with an early initiation of i.v. therapies with diuretics and vasoactive medication. Mentz et al. also emphasize the importance of early patient recruitment for the success of clinical trials. Future registries and trials should carefully define their selection criteria and assess new diagnostic and treatment strategies in patients with AHF very early after their presentation to the hospital’s emergency departments. This also requires that emergency departments are set up with resources that allow for high quality research in complex trials despite their very high work load.

Conclusions

Current populations with AHF from registries and clinical trials are the basis for evidence-based management strategies for patients with AHF. Due to varying criteria to define AHF, these populations have different characteristics and outcomes. Additionally, the timing of data collection and/or initiation of new therapies vary with the setting of trials.

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Conflict of Interest

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