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REVIEW

Steps forward in regulatory pathways for acute and chronic heart failure†

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Abstract

A workshop was organized by the Agenzia Italiana del Farmaco (AIFA) to discuss unmet needs and ways forward in the development of medicines in heart failure, their rationale, and cost-effective use. An integrated, multidisciplinary approach, including patients' needs and perspectives, was advocated by all the participants as the way to the most effective treatment regimens. More work is needed for reaching consensus on clinical and functional endpoints, for validating patient reported outcomes and measurements of well-being. Similarly, the integration into the clinical programmes of the health technology assessment/payers perspective, in particular, the evaluation of 'real-life' treatment effectiveness and of health as a value, would help in shifting the development and authorization of medicines from the molecule paradigm to their evaluation in the context of the whole health care regimen. Through this kind of workshop, AIFA is trying to build a template for meetings devoted to debate unmet needs with all stakeholders towards tentative road maps for the future.

Keywords Heart failure; Clinical trial design; Health technology assessment; Regulatory science

Introduction

In the last 15 years, few drugs have been approved for heart failure (HF), in front of an increasing demand of appropriate and better treatment with improved consequences for the patients. The approach to HF requires an even more multidisciplinary approach than currently seen to address patient needs and perspectives and develop a consensus on clinical and functional endpoints by an organized group of committed stakeholders with increased synergy. The management of HF requires a coordinated discussion among clinical, economic, and regulatory experts. The evaluation of the benefits of any new medicine for HF must address the many difficulties stemming from the large number of pathological aspects of several and different clinical diseases that develop as a part of HF.

On 24 and 25 November 2013, a meeting among Agenzia Italiana del Farmaco (AIFA), Heart Failure Association (HFA), and European Medicines Agency (EMA) representatives, clinicians, and other stakeholders had been organized at the AIFA headquarters in Rome.

Disease burden and current hurdles

HF[1,2] affects around 26 million people worldwide—6.5 million of which in European countries—and accounts for 1 million people hospitalized every year in Europe. Approximately 50% of patients with HF die within 4 years of diagnosis. The management of HF is not only directed at evaluating the clinical results but also linked to the costs of the treatment of the disease,[3] which shows significant differences in morbidity and mortality across Europe and the increasing needs in the cost–benefit ratio of multiple medical approaches. The current European Society of Cardiology (ESC) guidelines define HF as a complex syndrome, clinically characterized by signs and symptoms resulting from abnormality of the cardiac structure or function. Even though the wording varies slightly across articles and textbooks, the definition of HF remains a semeiotic and functional one, where 'abnormal' cardiac function is not a disease but the final common pathway of different conditions, among which the most common is ischaemic heart disease.[4]

The heterogeneity of aetiology and clinical and functional manifestations has a significant impact on the development of treatments for acute and chronic HF. Comorbidities entwined in the pathophysiology of HF such as coronary artery disease/ischemia, diabetes mellitus, depression and other neurological diseases, renal dysfunction, anaemia and iron deficiency, COPD, and cachexia[5,6] influence the design and the outcome of clinical trials. This is the case also of different clinical and functional phenotypes and of different stages of the disease. Several medicines failed in phase III after encouragingly positive phase II study results, with no new medicines for acute HF authorized in the past 15 years in Europe. The lack of consensus on key primary endpoints for evaluation (e.g. all-cause mortality or functional parameters); the lack of agreement on measurements of common features such as dyspnoea, functional capacity, and haemodynamic parameters as endpoints; and the uncertainty around the use of repeated events (e.g. hospitalization)[7–11] were discussed as some of the possible causes. The largest trials in HF are characterized by heterogeneity in primary endpoints and in the methodology and measurement of the same endpoint. It was recognized, among others, that the previous requirements of trials, including survival amongst the primary objectives before requesting an approval regardless of the type of product and the indication sought, might not always be the solution for all HF subpopulations.

The difficulty to show benefit of a new medicine on the signs and symptoms of HF on top of background therapy was recognized as another very important hurdle, with uncertainty from the developers on how to obtain consensus on optimal background therapy when evidence is limited and difficulties in the assessment of the efficacy by the regulators and of relative effectiveness by the payers when a new monotherapy is proposed on a background of complex, pharmacologic and non-pharmacologic interventions. The lack of consensus on the most appropriate outcome measures of functional assessment, disease progression, and preference between patients, care givers, and physicians adds burden and uncertainty to the trial designs in HF (Table *1*). In this landscape, the importance of patient reported outcomes (PROs) was acknowledged. Measurements of patients' status such as well-being, fatigue, mental confusion, and quality of life were considered relevant information in HF. However, there is at present a lack of validated PROs or quality of life instruments that can capture the disease and its changes from the patients' perspective and also remain suitable for integration into the regulatory pathway.

Evidence coming from randomized controlled trials is required before adopting therapeutic strategies, and biomarkers are used in this context as surrogate endpoints. From a regulatory perspective, biomarkers can be used

Table 1 The perspectives of the different stakeholders in the treatment of heart failure.

• The Different Perspectives
• Patient: I want to be offered whather can help me ***live longer***, ***feel better*** and ***treat the disease*** I have. I want my treatment to be affordable
• Physician: I want treatments that are safe, easy to use, ***easy to monitor*** and that protect and ***make my patients feel better***. I don't want ability to pay to be a barrier for my patients
• Developer: I want a ***clear predictable course*** to establish that a treatment works and what is required in terms of its risk profile. I want simple processes ***both*** for approval and for reimbursement
• Regulator: I want treatments to be safe, and to offer definite benefit, with the risk/benefit ratio clearly understood, ***and without excessive delay***
• Payer: I want a clear knowledge of ***what is gained for what cost***, so I can debate with my stakeholders what they wish to fund
Andrew Coats, Monash-Warwick Alliance

The bold italics are the priorities for each stakeholder.

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in the pre-clinical and clinical phase to guide different aspects of the development of a new medicine. The definition, purposes, and validity of biomarkers from the perspective of the regulators are the same as in the scientific community, with case-by-case requirements based on the specific question to be addressed (Figure *1*).

The role of biomarkers in the development and evaluation of new treatment approaches for HF is at present not very clear. While the diagnostic use of natriuretic peptides is well established, several difficulties limit the use of this and other biomarkers in clinical trials, including confounding from co-morbidities, in particular, renal failure, pulmonary embolism, and obesity.[12] In addition, even though a number of biomarkers have been associated with adverse outcomes across a variety of cardiovascular disease states including HF, they usually do not meet the criteria to support routine measurement for risk prediction in clinical practice and/or response to treatment.[13,14]

With limited centrally authorized medicinal products, the management of HF and its costs vary across Europe. The question then is whether payers use similar or consistent definitions and policies across Europe. If definitions and policies have significant differences, which policy is the most cost-effective? Moreover, what is the expected return of investment in treatment (in hospital or at home) from the public health and the pharmacoeconomic perspective? Understandably, the relative importance of each of these varies depending on the stakeholder interest (patients, developers, physicians, regulators, and payers), and central to this is the agreement on the definition of the 'value' of a treatment. It has been proposed that 'value in health care is measured by the outcomes achieved, not the volume of services delivered, and shifting focus from volume to value is a central challenge'.[15] Such a definition is suitable to include the pharmacoeconomic perspective of the value for money, such as health outcomes per dollar achieved, and at the same time broader views of value encompassing the importance or desirability that patients (or society) place on a health state. Value defined as outcomes relative to costs includes, among others, diagnostic efficiency in detecting and following up the disease and therapeutic 'real-life' effectiveness. The importance of the patients' global assessment and of its definition in relation to the management of the disease is central in a condition such as HF where the evaluation of effectiveness per se and in relation to costs is rendered difficult by the already mentioned clinical heterogeneity. The challenge faced by regulators including health technology assessment and by payers is how to include for reimbursement those medicines that are beneficial in a subset of patients while avoiding unnecessary expenses.

The pathway to drug development has been traditionally based on the sequence industry–regulators–payers/reimbursing agencies–prescribing physicians–patients. This pathway—lasting up to 10 years—has been shown to be exceptionally time costly in HF when one takes into account the poor output in terms of new effective treatments and the low level of innovation. In this scenario, the traditional role of the regulators of ensuring consistency in the development and authorization of medicines can be perceived as conservative and limiting. A number of advice and consultation instruments, such as the scientific advice during centralized procedures at EMA, are available within the regulatory system allowing for flexibility in the study designs, including in the case-by-case choice of endpoints beyond what is in a specific moment indicated in the regulatory guidelines. A strong association has been demonstrated between a positive outcome of a marketing authorization procedure and compliance with regulatory scientific advice.[16]

The centralized procedure in the field of HF is mandatory for medicinal products derived from biotechnology processes and for advanced therapies, such as gene therapy, somatic cell therapy, or tissue-engineered medicines. For other types of products, a sponsor can choose between a national or centralized marketing authorization. Among the products currently in the scientific advice phase at EMA, old product classes still dominate the scene; however, a number of new products are being developed

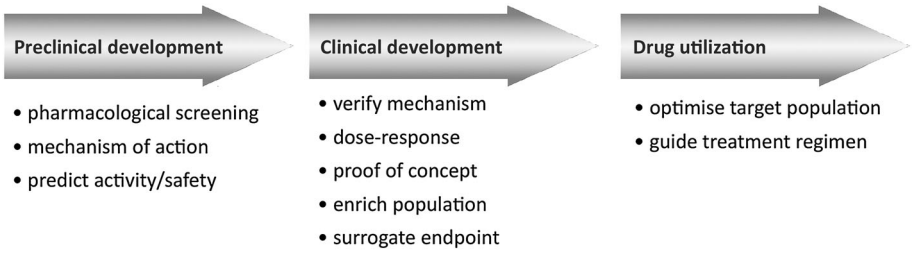

Figure 1 Use of biomarkers to regulatory purposes.

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including innovative approaches such as gene therapy and cell-based treatments. The clinical heterogeneity, the lack of 'one size fits all' endpoints, and the complex and multidisciplinary matrix of interventions to be taken into account for relative effectiveness make of HF a good case study for different regulatory pathways, including, for example, possible adaptive licensing approaches. Discussion is ongoing about adaptive licensing concepts and contents at European level in the regulatory field. Central to the discussion are the methodology and assessment of the possible ways to capture 'real-life' data. Observational studies, pragmatic trials, and other methods for efficacy studies in the everyday medical practice, including the use of registries as data sources, can offer the basis for such information; however, consensus has to be built around remits, merits, and limitations of this type of studies in the framework of the regulatory adaptive mechanisms.

Steps forward

There is the need to rethink the traditional approach for the development of medicines for acute and chronic HF, taking into greater account of the heterogeneous pathophysiology of the condition. Understanding the characteristics and needs of the single patient in the different phases of HF is also crucial, together with identification of genetic, functional, and/or clinical phenotypes, in order to 'match the medicine with the right patient'. This is acknowledged in the guidelines on acute HF from the scientific societies and the regulators.[6,17] In this view, more efforts are needed in investigating the genetic factors predisposing to HF and factors linked to different responses to drugs, opening the possibility to stratify patients into, for example, likely responders, likely non-responders, or those likely to experience adverse reactions.[18]

The identification of phenotypic correlates of genetic variations is particularly important when it comes to designing appropriate clinical trials, and in this perspective, the challenge for the scientists and the regulators will be that of managing, analyzing, and assessing the 'fitness for purpose' of the large amount of data being generated by genomic-wide association studies and by the quest for -omics. In relation to phenotyping, the review of the experience from completed trials, including those that failed in phase III, is a useful starting point for the identification of subpopulations of patients characterized by different clinical responses and patients at high risk.

Similarly, critical appraisal of the existing trials can help in identifying the best definitions and methodology for endpoints. The need to move beyond the established targets and to validate reproducible and specific measurements of function, disease progression, and quality of life or patient preference was advocated. This, in some case, would also imply tailoring the use of mortality as an endpoint, especially in trials on chronic HF and in populations at low-risk/slow progression. The development of endpoints based on quantitative measurements of function is central vs. non-specific symptom endpoints such as dyspnea,[19] which is one of the most difficult endpoints to standardize and is easily confounded by co-morbidities. Similarly, there is at present insufficient detail of usefulness of data supporting PRO-based treatments and in relation to outcome. The validation of PROs and their value in the evaluation of treatments for HF need to be better defined through specific studies. Studies on cardiac cell-based repair and regeneration with potential for later translation into clinical studies in the future are also needed in order to establish the most valid designs and endpoints for the outcome of tissue regeneration in HF.

The importance of stimulating research on biomarkers related to survival or other clinically relevant endpoints was underlined. Ideally, changes in biomarkers would be validated against specific disease phenotypes, including, for example, imaging-based and clinical, before being tested in large-scale therapeutic studies. A process of biomarker qualification is provided at the EMA and can be performed on diagnostic and prognostic biomarkers and on companion diagnostic biomarkers. Increasing the use of this type of programme can provide a way to maximize resources and synergies in the assessment of the methodology and validity criteria of the proposed biomarkers. Besides biomarkers, qualification can be asked for novel methodological approaches to trial design and analysis including modelling and simulations. The centralized procedure for the authorization of new products might also help in increasing consistency in clinical trials because it encompasses meetings with a wide range of pre-clinical and clinical experts, therefore allowing discussion at the state of the art of science and regulatory medicine. In this view, it is also important to increase efforts for harmonizing academic and regulatory guidelines.

The addition of endpoints and methodology useful to the assessment of relative effectiveness was seen as very important for better designing the overall management of HF and improving quality of care in HF because of the complex matrix management that includes, besides medicinal products, devices and life style measures.

In this perspective, the best solution for developing and evaluating new medicines does not necessarily lie

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in one single type of study or model, but in combining information from different types of studies along the pre-authorization and post-marketing life cycle of medicinal products. A possible approach to adaptive ways of licensing a new product for HF could include post-approval extension of endpoints, for example, evaluating the impact of the product in real life on mortality and on additional endpoints relevant to relative effectiveness. Similarly, the use of the product in its post-marketing life in the frame of specifically designed studies could allow better defining the target patient population (Figure *2*). The creation of a case study in HF for testing the integration of different points of view in the development of a new product was seen as a good opportunity for advancing the field.

In conclusion, a multidisciplinary approach, including integration of patients' needs and perspective, was advocated by all participants as the way to new effective medical treatment of HF. Effort is needed for reaching consensus on clinical and functional endpoints and for identifying and validating relevant PROs. The integration into clinical programmes of the health technology assessment/payers perspective, with the evaluation of relative effectiveness and of health value, would help in shifting from the 'single molecule' paradigm towards the evaluation of medicinal products in a wider health care perspective, with the aim of improving at the same time the development of medicinal products and of the quality of care. Figure *3* presents a strengths, weaknesses, opportunities, and threats (SWOT)-type analysis for drug development in HF resulting from the 2-day discussion.

Through this kind of workshop, AIFA is trying to build a template for meetings devoted to debate unmet needs with all stakeholders towards tentative road maps for the future.

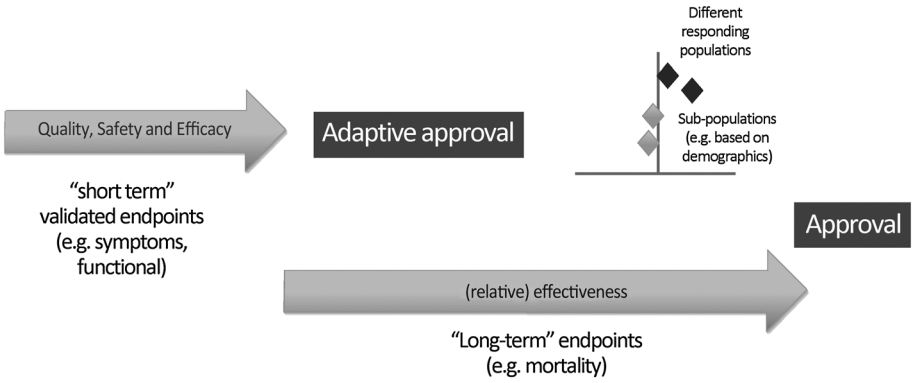

Figure 2 Visualization of an adaptive licensing approach to new medicinal products.

S	W
All stakeholders in one room	Definition of HF (phenotypes?)
Basic science & clinical experts	No role models
Experience from completed trials	End-points
Experienced trial sites	Little/no interaction between stakeholders
O	**T**
HF treatable & unmet need	Low awareness
Adaptive trial design/licensing	Different perspectives&barriers
Patient related outcomes	Trial complexity
HF organisations	Reimbursment &system sustainability
Iinvestigator initiated trials	Definition of values
Biomarkers (adopt regulatory requirements)	

modified from Mitja Lainščak, University Clinic Golnik (Slovenia)

Figure 3 Analysis of Strengths, Weaknesses, Opportunities and Threats (SWOT) for drug development in heart failure. ***Participants voted for the most important issues (reference for the SWOT method).***

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Disclaimer

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