The vulnerable phase of heart failure: a window of opportunity

“Chance favors only the prepared mind.”

Pasteur

Vol 37, No. 2, 2015
The vulnerable phase of heart failure: a window of opportunity

EDITORIAL
119 Hospitalization for heart failure: can we prevent it? Can we predict it?
Hospitalisation pour insuffisance cardiaque : pouvons-nous la prévenir ?
Pouvons-nous la prévoir ?
M. Komajda, France

THEMED ARTICLES
125 The changing landscape of heart failure outcomes
J. López-Sendón, N. Montoro, Spain

135 The social and economic burden of hospitalization for heart failure
D. Farmakis, G. Filippatos, J. Parissis, J. Lekakis, Greece

139 Postdischarge outcomes of patients hospitalized for heart failure
M. Metra, V. Carubelli, I. Castrini, A. Ravera, E. Sciatti, C. Lombardi, Italy

144 Definition and characteristics of the vulnerable phase in heart failure
M. B. Yilmaz, A. Mebazaa, Turkey and France

149 Treatment optimization in heart failure patients from admission to discharge
P. Ponikowski, E. A. Jankowska, Poland

155 Postdischarge assessment and management of patients with heart failure
M. R. Cowie, United Kingdom

163 Impact of quality improvement initiatives in patients hospitalized for heart failure
J. L. Zamorano, V. C. Lozano, Spain
CONTROVERSIAL QUESTION

171 Can biomarkers guide the assessment and management of heart failure patients after discharge from hospitals?
E. A. Bocchi, Brazil - D. A. Brito, Portugal - O. Chioncel, Romania - A. Fong, Malaysia - M. Hülsmann, Austria - E. A. Jankowska, Poland - M. Loutfi, Egypt - A. Lupi, Italy - Y. F. M. Nosir, Egypt - E. B. Reyes, Philippines - S. N. Tereschenko, Russia - M. B. Yilmaz, Turkey - B. Yoo, Republic of Korea

PROCORALAN

185 Procoralan: new opportunities for vulnerable heart failure patients
I. Elyubaeva, France

INTERVIEW

193 Therapeutic education: which tool for whom?
P. Jourdain, France

FOCUS

197 Challenges in predicting heart failure readmission: focus on heart rate
M. Böhm, Germany

UPDATE

202 Telemonitoring in heart failure management: what is needed to make it fit for routine use?
C. Zugck, Germany

A TOUCH OF FRANCE

210 MuCEM, the pride of Marseille
M. Raive, France
221 The Medical Faculty of Montpellier: one thousand years of medicine
C. Régnier, France
Heart failure is a common condition associated with poor outcomes. Its prevalence is increasing worldwide for several reasons, including aging of the population, and this situation raises concerns about the growing burden for health care systems. Significant progress has been made in the pharmacological management of chronic heart failure over the last decades; this is due to the introduction of angiotensin-converting enzyme (ACE) inhibitors, β-blockers, angiotensin receptor blockers, mineralocorticoid receptor antagonists, and more recently the current blocker ivabradine. This has resulted in a significant reduction in heart failure–related mortality. The annual death rate was approximately 20% before the era of ACE inhibitors, whereas in the most recent trials, this rate has been reduced to 5% to 10%. Importantly, this is observed not only in clinical trials, which include selected populations, but also in the general population.

However, the fact that the impact of modern therapies does not translate into a significant reduction in heart failure–related hospitalizations is a cause for concern. Some publications actually suggest a bidirectional trend in which there is a reduction in mortality and an increase in hospitalizations. This is all the more worrisome as the cost of heart failure hospitalizations accounts for approximately 70% of all the expenses incurred in the management of heart failure, since heart failure hospitalizations are both lengthy and recurrent. Several explanations can be put forward in order to explain this apparent paradox. First, severely affected patients now survive thanks to modern therapy at the expense of (re)hospitalizations with a particularly critical phase in the first 30 days that follow an index hospitalization. Second, uptitration of lifesaving medications remains suboptimal. In fact, recent surveys suggest that the rate of prescription of the medications recommended by international guidelines has improved, whereas the titration of these drugs is not performed in practice. For instance, a recent survey carried out across European Society of Cardiology countries shows that, overall, only 25% to 30% of patients reach the target recommended dose of β-blockers in real-life situations. Multiple comorbidities are frequent in elderly patients with heart failure, and they can result in contra/indications or poor tolerance of some of the recommended medications. This is, however, only part of the explanation for the reluctance of health care professionals to uptitrate these treatments in the context of polypharmacy, as complex uptitration schemes also play a significant role. Third, patients who have recently been hospitalized for heart failure decompensation are not appropriately monitored by health care professionals. There is often a gap in follow-up care after discharge and many patients do not see any health care professional (cardiologists, general practitioners, or specialized nurses) at a time when the risk of being rehospitalized for decompensation is extremely high.
In some surveys, less than one-third of patients hospitalized for heart failure were found to have consulted a cardiologist in the first 3 months after discharge. This poor coordination is one of the major reasons why titration of lifesaving medications initiated in hospital during the decompensation phase is not continued afterwards. A fundamental issue is, therefore, to find solutions in order to improve this situation.

**Better education**

In-depth information on the challenges and objectives of the treatment of a chronic condition such as heart failure should target the professionals in charge of its long-term management. This applies particularly to general practitioners who, in many circumstances, are responsible for the uptitration of medications outside the hospital. Here, the role of international guidelines is critical in order to provide clear guidance and information in an abridged version and convince professionals of shifting the primary goal of treatment from symptom relief to improvement of outcomes. Pocket versions of guidelines such as those developed by the European Society of Cardiology are typically appropriate for this.

We have, however, to acknowledge the existence of gaps in evidence in the field of heart failure. In particular, in heart failure with preserved ejection fraction—which represents a growing proportion of heart failure patients—there is scarce evidence of benefits with any cardiovascular drug, and therefore, we cannot provide evidence-based recommendations for these patients. Patient education is also key for success: detailed information on the disease, treatment objectives, warning signals of decompensation, side effects of medications, and dietary requirements should be provided by physicians as well as nurses and nutritionists. This is the best way to make patients aware of the potential mistakes that can lead to decompensation such as poor compliance with medications or excessive sodium intake.

Patient education is often provided individually in an unstructured manner. It is, however, preferable to adopt standardized strategies in specific structures where all the professionals mentioned above can interact with small groups of heart failure patients using visual tools in lay language in order to facilitate communication. Several national programs have been successfully conducted in this way. The ultimate goal of this strategy is to transform the relationship between the patient and the health care professional(s) into a partnership where the patient plays an active role.

**Better cooperation between health care professionals**

Management of heart failure after discharge varies considerably between countries: cardiology departments, internal medicine divisions, and specialized heart failure clinics can all be responsible for coordinating care management as well as private cardiologists, general practitioners, or specialized nurses.

There is, therefore, no unique solution to improve the somewhat fragmented journey of the heart failure patient. However, it appears necessary to develop better communication and coordination between stakeholders. Idealy, this can take place in structured multidisciplinary networks as they have been shown to improve (re)hospitalization rates.

**Biomarkers monitoring and telemonitoring**

Several studies suggest that serial measurements of natriuretic peptide plasma level can lead to a significant improvement in outcomes. A recent meta-analysis of these studies shows that natriuretic peptide-guided strategies can reduce hospitalizations for heart failure by approximately 25% compared with standards of care. Of note, although this natriuretic peptide-guided strategy had beneficial effects on mortality in younger patients <75 years, it did not in those >75 years, who represent the majority of heart failure patients.

Another strategy is to use telemedicine. This generic term covers very different situations, from structured telephone support to remote distance monitoring of biomarkers such as weight, heart rate, blood pressure, oximetry, electrocardiogram, or estimated pulmonary blood pressure through sophisticated implantable devices. The results of published studies show some divergence, but a meta-analysis of these trials suggests nevertheless that telemedicine could improve outcomes and, in particular, reduce heart failure–related hospitalizations. In many countries though, integration of this novel approach to classic in-hospital existing structures is unresolved and reimbursement of the time spent by professionals for these activities remains an issue.

**Conclusion**

In summary, the management of chronic heart failure with reduced ejection fraction has significantly improved the rate of mortality related to this condition. However, the burden of rehospitalizations remains an important issue: it is associated with a very poor quality of life and it puts health care systems under considerable strain. One of the major reasons for this situation is underdosing of recommended medications and insufficient implementation of guidelines. It results from non-modifiable factors related to patient conditions (age, comorbidities, and related contraindications), but also from the fragmented organization of health care systems. In order to improve the situation we need to recognize that the management of this chronic condition is a continuum and that postdischarge treatment and follow-up are as important as in-hospital management. A better global organization of medical care around the heart failure patient is needed and health economic assessment of new initiatives is warranted in order to select optimal strategies.

This issue of Medicographia reviews all the scientific questions related to the management of heart failure, and in particular, the transition from hospital care to postdischarge management.
References

Keywords: heart failure; hospitalization; prevention; postdischarge management
ÉDITORIAL

...la charge des réhospitalisations constitue toujours un problème important : elle est associée à une qualité de vie très dégradée et elle exerce une charge considérable sur les systèmes de soins de santé. L’une des principales raisons de cet état de fait est le sous-dosage des médicaments recommandés et la mise en œuvre insuffisante des directives. Les raisons proviennent de facteurs non modifiables liés aux patients (âge, comorbidités et leurs contre-indications inhérentes), mais également de l’organisation fragmentée des systèmes de soins de santé.

Hospitalisation pour insuffisance cardiaque : pouvons-nous la prévenir ? Pouvons-nous la prévoir ?

par M. Komajda, France

L’insuffisance cardiaque est une affection fréquente dont l’évolution est défavorable. Sa prévalence augmente à travers le monde pour plusieurs raisons, notamment le vieillissement de la population, et cette situation soulève un certain nombre de problèmes concernant la charge croissante assumée par les systèmes de soins de santé. Des progrès significatifs ont été accomplis dans la prise en charge pharmacologique de l’insuffisance cardiaque chronique au cours des dernières décennies ; cette amélioration est due à la mise sur le marché des inhibiteurs de l’enzyme de conversion de l’angiotensine (IEC), des bétabloquants, des antagonistes des récepteurs de l’angiotensine, des antagonistes des récepteurs des minéralocorticoïdes et plus récemment de l’ivabradine, un inhibiteur du courant If. D’où une réduction significative de la mortalité liée à l’insuffisance cardiaque. Le taux de mortalité annuel était d’approximativement 20 % avant l’apparition des IEC, alors que les études les plus récentes ont montré une réduction de ce taux de 5 % à 10 %. Il est important de souligner que ce résultat a été observé non seulement dans les études cliniques, qui portent sur des populations sélectionnées, mais également dans la population générale.

Cependant, le fait que l’impact des traitements modernes ne se traduise pas en une réduction significative des hospitalisations pour insuffisance cardiaque soulève un certain nombre de problèmes. Plusieurs publications suggèrent même une tendance bidirectionnelle, c’est-à-dire une réduction de la mortalité et une augmentation des hospitalisations. Cette observation est particulièrement préoccupante, car le coût des hospitalisations pour insuffisance cardiaque représente environ 70 % de l’ensemble des dépenses liées à la prise en charge de l’insuffisance cardiaque, dans la mesure où les séjours dus à une insuffisance cardiaque sont à la fois longs et récurrents. Plusieurs explications peuvent être avancées pour expliquer ce paradoxe apparent. Tout d’abord, les patients sévèrement affectés survivent désormais grâce aux traitements modernes aux dépens de (ré)hospitalisations, une phase particulièrement critique intervenant au cours des 30 premiers jours suivant l’hospitalisation initiale. Ensuite, l’augmentation posologique des médicaments essentiels reste sousoptimale. En fait, de récentes enquêtes suggèrent que le taux de prescription des médicaments recommandés par les directives internationales s’est amélioré, mais que l’ajustement posologique de ces médicaments n’est pas effectué en pratique. Par exemple, une étude réalisée récemment dans les pays de la Société Européenne de Cardiologie montre que d’une manière générale, seulement 25 % à 30 % des patients atteignent la dose cible recommandée pour les bétabloquants en pratique réelle. Les patients âgés atteints d’insuffisance cardiaque présentent fréquemment de multiples comorbidités qui peuvent entraîner des contre-
indication ou une mauvaise tolérance à certains des médicaments recommandés. Cependant, cela n’explique que partie de la résistance des professionnels de santé à augmenter la posologie de ces traitements dans le contexte d’une polymédicalisation ; en effet, la complexité des schémas d’augmentation posologique peut également jouer un rôle significatif. Ensuite, les patients ayant récemment été hospitalisés pour une insuffisance cardiaque décompensée ne sont pas surveillés de manière appropriée par les professionnels de santé. Les soins de suivi après la sortie de l’hôpital vont souvent une discontinuité, et un grand nombre de patients ne consultent aucun professionnel de santé (cardiologue, médecin généraliste ou infirmière spécialisée) au cours d’une période où le risque de réhospitalisation pour décompensation est extrêmement élevé.

Dans certaines études, moins d’un tiers des patients hospitalisés pour insuffisance cardiaque ont consulté un cardiologue au cours des 3 premiers mois ayant suivi la sortie de l’hôpital. Cette mauvaise coordination est l’une des raisons majeures qui expliquent pourquoi l’augmentation posologique des médicaments essentiels mise en œuvre à l’hôpital au cours de la phase de décompensation n’est pas poursuivie par la suite. Il est par conséquent fondamental de trouver des solutions permettant d’améliorer cette situation.

Une meilleure formation
Une information approfondie sur les difficultés et les objectifs du traitement d’une affection chronique, comme l’insuffisance cardiaque, doit cibler les professionnels chargés de sa prise en charge à long terme. Cela est particulièrement vrai pour les médecins généralistes qui, dans de nombreuses circonstances, ont la charge de l’augmentation posologique des médicaments lorsque le patient n’est plus hospitalisé. Le rôle des directives internationales est à cet égard essentiel, car elles doivent fournir une orientation claire et des informations concises destinées à convaincre les professionnels de changer l’objectif primaire du traitement, consistant à soulager les symptômes et à améliorer les résultats. Des versions des directives en format poche, comme celles développées par la Société européenne de cardiologie, sont particulièrement adaptées à cette situation.

Nous devons cependant reconnaître que les données sur l’insuffisance cardiaque dont nous disposons présentent certaines lacunes. En particulier, dans l’insuffisance cardiaque avec fraction d’éjection préservée – qui représente une proportion croissante des patients insuffisants cardiaques – peu de bénéfices ont été mis en évidence avec les différents traitements cardio-vasculaires, et il est par conséquent impossible de fournir des recommandations factuelles pour cette population de patients. L’éducation des patients est également essentielle à la réussite : des informations détaillées sur la maladie, les objectifs thérapeutiques, les signaux d’alerte d’une décompensation, les effets indésirables des médicaments et les recommandations alimentaires doivent être délivrés par les médecins, ainsi que par les infirmières et les nutritionnistes. C’est la meilleure manière de faire prendre conscience aux patients que certaines erreurs éventuelles peuvent conduire à une décompensation, par exemple une mauvaise observance du traitement médicamenteux ou une consommation excessive de sodium.

L’éducation des patients est souvent délivrée individuellement de manière non structurée. Il serait pourtant préférable d’adopter des stratégies standardisées dans des structures spécifiques, où tous les professionnels mentionnés ci-dessus pourraient interagir avec de petits groupes de patients insuffisants cardiaques, en utilisant des outils visuels dans un langage simple destinés à faciliter la communication. Plusieurs programmes nationaux ont été menés avec succès dans cet esprit. L’objectif ultime de cette stratégie est de transformer la relation entre le patient et les professionnels de santé en un partenariat dans lequel le patient joue un rôle actif.

Une meilleure coopération entre les professionnels de santé
La prise en charge de l’insuffisance cardiaque après la fin de l’hospitalisation est extrêmement variable selon les pays : les services de cardiologie, les services de médecine interne et les cliniques spécialisées dans l’insuffisance cardiaque sont tous susceptibles d’assurer la responsabilité de la coordination des soins, de même que les cardiologues privés, les médecins généralistes ou les infirmières spécialisées. Il n’existe donc aucune solution unique permettant d’améliorer le parcours quelque peu fragmenté du patient insuffisant cardiaque. Cependant, il apparaît nécessaire de développer une meilleure communication et une coordination efficace entre les différents intervenants. Dans l’idéal, cela pourrait être mis en œuvre dans des réseaux multidisciplinaires structurés, dans la mesure où il a été démontré qu’ils amélioraient les taux de (ré)hospitalisation.

Surveillance et télésurveillance des biomarqueurs
Plusieurs études suggèrent que des mesures en série des concentrations plasmatiques de peptide natriurétique pourraient entraîner une amélioration significative des résultats. Une récente méta-analyse de ces études a montré que les stratégies guidées par le peptide natriurétique permettaient de réduire les hospitalisations pour insuffisance cardiaque d’environ 25 %, par rapport aux soins standard. Il faut souligner que cette stratégie guidée par le peptide natriurétique a des effets bénéfiques sur la mortalité des patients âgés de moins de 75 ans, mais non chez ceux âgés de plus de 75 ans, qui représentent pourtant la majorité des patients atteints d’insuffisance cardiaque.

Une autre stratégie repose sur l’utilisation de la télémédecine. Ce terme général peut recouvrir des situations très variables, pouvant aller d’un soutien téléphonique structuré à une sur-
veillance à distance des biomarqueurs, notamment le poids, la fréquence cardiaque, la pression artérielle, l’oxymétrie, l’électrocardiogramme ou la pression artérielle pulmonaire estimée à l’aide de dispositifs implantables sophistiqués. Les résultats des études publiées montrent certaines divergences, mais une méta-analyse de ces études suggère néanmoins que la télémédecine pourrait améliorer les résultats et, en particulier, réduire les hospitalisations liées à une insuffisance cardiaque9. Toutefois, dans de nombreux pays, l’intégration de cette nouvelle approche aux structures existantes d’hospitalisation classiques n’est pas résolue, et le remboursement du temps passé par les professionnels pour ces activités constitue toujours un problème.

Conclusion
En résumé, la prise en charge de l’insuffisance cardiaque chronique avec réduction de la fraction d’éjection a significativement amélioré le taux de mortalité lié à cette affection. Cependant, la charge des réhospitalisations constitue toujours un problème important : elle est associée à une qualité de vie très dégradée et elle exerce une charge considérable sur les systèmes de soins de santé. L’une des principales raisons de cet état de fait est le sous-dosage des médicaments recommandés et la mise en œuvre insuffisante des directives. Les raisons proviennent de facteurs non modifiables liés aux patients (âge, comorbidités et leurs contre-indications inhérentes), mais également de l’organisation fragmentée des systèmes de soins de santé. Afin d’améliorer cette situation, nous avons besoin de reconnaître que la prise en charge de cette affection chronique suit un continuum, et que le traitement et le suivi post-hospitalisation sont aussi importants que la prise en charge hospitalière. Une meilleure organisation globale des soins médicaux centrés sur le patient insuffisant cardiaque est nécessaire, et une évaluation pharmacoéconomique des nouvelles initiatives doit être effectuée pour sélectionner les stratégies optimales.

Ce numéro de Medicographia passe en revue l’ensemble des questions scientifiques liées à la prise en charge de l’insuffisance cardiaque et, plus particulièrement, la transition entre les soins hospitaliers et la prise en charge du patient après sa sortie de l’hôpital.

Mots clés : insuffisance cardiaque; hospitalisation; prévention; prise en charge après la sortie de l’hôpital.
Heart failure is a highly prevalent, lethal, and costly condition. For many years, treatment was focused on improvement of symptoms. Sodium restriction, diuretics, digoxin, and nitrates were the principal (and only) therapies employed to alleviate symptoms and improve functional capacity. Then, the CONSENSUS trial (COoperative North Scandinavian ENalapril SUrvival Study) demonstrated that medical therapy could also prolong life, a concept that changed clinical practice and research objectives in heart failure. Since then, β-blockers, angiotensin II receptor blockers, aldosterone antagonists, and Iv current blockers were included in the first-line treatment of patients with heart failure, along with nonmedical therapies such as implantable defibrillators, resynchronization, and other therapeutic strategies that also demonstrated a clear benefit in outcomes of selected populations. Research has been intensive and fraught with failures. The majority of major clinical trials have yielded neutral or even negative results. Trials with inotropic drugs, antiarrhythmic drugs, some vasodilators, and other drugs had to be prematurely discontinued because of an unexpected increase in mortality. Nevertheless, the landscape of heart failure treatment has changed completely. Guidelines have been prepared to recommend evidence-based therapies to improve survival and reduce hospitalization. Research continues, but the immediate challenge is to follow the guidelines' recommendations for treatments that prolong survival, reduce hospitalization, and improve ventricular function and quality of life.

Address for correspondence:
José López-Sendón, MD
Hospital Universitario La Paz
IdiPaz Research Institute
Madrid, SPAIN
(e-mail: jlopezsendon@gmail.com)
www.medicographia.com
The changing landscape of heart failure outcomes – López-Sendón and Montoro

Figure 1. Hospitalizations for heart failure in Europe and the United States. All data shown include planned admissions. Abbreviations: HF (1º/2º), number of hospitalizations for heart failure as primary/secondary diagnosis; HF (any), number of hospitalizations for heart failure as any diagnosis; HF/total, heart failure hospitalizations as a proportion of all hospitalizations; LOS, average length of hospital stay; Total, total number of hospitalizations.

Table I. Heart failure burden in numbers. Based on data from various sources.

<table>
<thead>
<tr>
<th>Year of heart failure</th>
<th>Prevalence (%) of heart failure</th>
<th>Direct costs of heart failure</th>
<th>Indirect costs of heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>2.8</td>
<td>24.7</td>
<td>9.7</td>
</tr>
<tr>
<td>2015</td>
<td>3.0</td>
<td>32.4</td>
<td>11.3</td>
</tr>
<tr>
<td>2020</td>
<td>3.1</td>
<td>42.9</td>
<td>13.0</td>
</tr>
<tr>
<td>2025</td>
<td>3.3</td>
<td>57.5</td>
<td>15.1</td>
</tr>
<tr>
<td>2030</td>
<td>3.5</td>
<td>77.7</td>
<td>17.4</td>
</tr>
<tr>
<td>% Change</td>
<td></td>
<td>215</td>
<td>80</td>
</tr>
</tbody>
</table>

The long-term prognosis associated with heart failure is poor. The causes of death without improving overall prognosis simply imply a terrible social and economic burden. The control of communicable diseases, such as diabetes and obesity, we may see a greater increase in cardiovascular diseases, heart failure, and associated costs. In countries with an economy in transition, there may be more dramatic eventualities. The control of communicable diseases, the expected steep increase in life expectancy, and the change in lifestyle mainly due to a shift from rural to urban communities may lead to a steady increase in cardiovascular diseases, such that the heart failure pandemic will be, simply, global. The only solution to prevent this growing epidemic is through control of risk factors.

Accurate diagnosis is one of the major issues in heart failure. Symptoms may be misleading. The diagnosis of heart failure with depressed systolic ventricular function is elusive and the correct diagnosis of diastolic heart failure is a real clinical challenge. This chapter focuses on outcomes in general, though the evidence in the literature mainly refers to heart failure with depressed left ventricular ejection fraction.

**Outcomes in heart failure**

The aim of therapies in heart failure is to prolong life, reduce hospitalization, and improve functional capacity. These main outcomes have been the target and have served as measures of efficacy in therapies for clinical trials in heart failure. Table III (page 128) details the most important outcomes in heart failure, along with their advantages and drawbacks in clinical practice and in clinical trials.

**Mortality**

The long-term prognosis associated with heart failure is poor. Half of all patients diagnosed with heart failure die within 4 years, and the 5-year survival rate is lower than that associated with myocardial infarction and the majority of key malignancies. Accordingly, mortality has been the most important outcome to be included in clinical trials. The importance of total mortality is self-evident, but includes heart failure-related as well as other cardiovascular and noncardiovascular mortalities. This may be important in patients with heart failure and preserved systolic function, a clinical setting where comorbidities have an important impact on outcomes, making the evaluation of therapy strategies very difficult in this form of heart failure. Sudden death is the single most common form of death in heart failure, but decreasing sudden death without improving overall prognosis simply implies a change in the mode of death and is a useless achievement. Mortality directly related to heart failure itself is probably the best single outcome measure to evaluate the efficacy of new therapies and should be included in all heart failure trials designed to explore outcomes. The main problem with this outcome measure is the need for adjudication, as comorbidities often contribute to the cause of death.

**Hospitalization**

Hospitalization for heart failure is now recognized to be one of the most important outcomes in cardiology. Worsening heart failure resulting in hospitalization may be associated with cardiac and/or renal injuries that may contribute to progression of heart failure, comorbidities, changes in lifestyle, and compliance with medication. Hospitalizations are associated with unacceptably high postdischarge mortality and rehospitalization rates and are the single most important parameter related to cost of care in heart failure patients. Besides, the need for hospitalization objectively defines quality of life. However, hospitalization for heart failure itself is difficult to ascertain, and is influenced by social, cultural, and economic reasons.

Nevertheless, hospitalization remains one of the principal outcome measures and should be included in all clinical trials evaluating outcomes in this population. Comprehensive planning of hospital discharge, adequate patient education, and initiation and continued optimization of disease-modifying therapies are crucial opportunities for improving postdischarge outcomes and preventing repeated events in these patients.

**Other clinical outcomes**

Stroke and myocardial infarction are relatively frequent in patients with heart failure and have been included in some outcome trials, but the relationship with heart failure therapies is uncertain. Undoubtedly, renal failure plays a key role in the progression of the disease. It is associated with hospitalizations and prognosis and may be a target for treatment; however, some therapies may have an adverse influence on renal function. Renal function is not a clinical outcome itself except when it forces hospitalization, dialysis, or other clinically relevant action, and this should be included as a clinical outcome measure in patients with heart failure.

**Symptoms and quality of life**

Improvement in functional capacity and reduction in symptoms may be perceived as the most important target for many patients with heart failure and will remain among the top priorities in the measurement of outcomes for this condition.
<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major clinical outcomes</td>
<td>Accepted and used in most major trials. Reduction in major outcomes is still needed in clinical practice.</td>
</tr>
<tr>
<td>Total mortality</td>
<td>Self-evident. Includes death possibly related to secondary effects of therapies.</td>
</tr>
<tr>
<td>Sudden death</td>
<td>Self-evident.</td>
</tr>
<tr>
<td>Hospitalization and rehospitalization</td>
<td>Probably best parameter for quality of life assessment. High impact in cost.</td>
</tr>
<tr>
<td>Stroke, myocardial infarction</td>
<td>Self-evident</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Directly related with heart failure progression and outcomes. Therapies may worsen renal function.</td>
</tr>
<tr>
<td>Other clinical outcomes</td>
<td>Would reduce the population needed in clinical trials.</td>
</tr>
<tr>
<td>Symptom improvement, quality of life</td>
<td>May be the primary choice of the patient.</td>
</tr>
<tr>
<td>Need of ventilator support, dialysis, ventricular assist device</td>
<td>Physician dependent.</td>
</tr>
<tr>
<td>Surrogates for outcomes</td>
<td>Use of surrogates (parameters related to major outcomes) would greatly reduce the number of patients needed to demonstrate benefit of therapies in heart failure trials.</td>
</tr>
<tr>
<td>Ventricular function, eg, LVEF</td>
<td>Easy to measure.</td>
</tr>
<tr>
<td>Hemodynamic improvement</td>
<td>Related to symptom improvement.</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td></td>
</tr>
<tr>
<td>Number of days in ICU</td>
<td>Relevant, cost related.</td>
</tr>
<tr>
<td>Need of ventilator support, dialysis, ventricular assist device</td>
<td>Physician dependent.</td>
</tr>
<tr>
<td>BNP</td>
<td>Easy to measure, recommended for diagnosis of heart failure.</td>
</tr>
<tr>
<td>Diuresis and other biomarkers</td>
<td>Relationship with symptom improvement. Congestion considered as first cause for hospitalization.</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Related to prognosis.</td>
</tr>
<tr>
<td>Safety (EMA criteria)</td>
<td></td>
</tr>
</tbody>
</table>

Mortality (over 6 months), arrhythmias, corrected QT interval (QTc), hypotension, ischemic events, renal function (over 6 months), bradycardia and atrioventricular (AV) conduction disturbances, exaggerated pharmacological response in special groups (children, women, elderly)
However, neither functional capacity nor symptom improvement has been related to major outcomes, and symptoms are subjective and difficult to evaluate. For these reasons, symptoms and functional capacity will probably remain to be considered important, but second-line, outcomes in the measurement of therapy efficacy.

◆ No surrogates in heart failure?
Surrogates are parameters related to major outcomes. Improvements in these parameters would have a favorable impact on clinical outcomes. An example would be hypercholesterolemia and hypertension. Both are well-recognized prognostic factors and reducing hypercholesterolemia and hypertension levels improves outcomes.

For years, surrogates in heart failure have been a deception. Many therapies that improve symptoms, ventricular function, and arrhythmias related to sudden cardiac death, and even therapies that decrease neurohormonal activation not only failed to demonstrate a benefit, in some cases they were associated with an increase in mortality. The lack of reliable surrogates is one of the most important barriers to identifying new therapies in heart failure.

More recently, it has been demonstrated that B-type natriuretic peptide levels (BNP and N-terminal proBNP) are increased in heart failure and are closely related with prognosis. Changes in BNP levels may represent a reliable surrogate, but this concept is still controversial.

Heart rate is clearly related to outcomes in heart failure and heart rate reduction has been associated with an improvement in outcomes. Furthermore, heart rate reduction induced with ivabradine, with no inotropic or vasoactive effects, improved outcomes in the SHIFT trial (Systolic Heart failure treatment with the i, inhibitor ivabradine Trial), reducing heart failure mortality and the need for hospitalization and recurrent hospitalizations as well as improving ventricular function and quality of life. The information available supports the concept of heart rate as a reliable surrogate for outcomes in heart failure; in fact, it may be considered not only as a prognostic factor, but also as a therapeutic target.

◆ Safety
With more aggressive therapies and multiple-drug combinations, safety becomes an issue in patients with heart failure and different parameters must be monitored during follow-up. These include all types of secondary effects previously reported in patients with heart failure; among others: mortality (over 6 months) in trials not designed to measure outcomes, arrhythmias, corrected QT interval (QTc) prolongation, hypotension, ischemic events, renal function (over 6 months), bradycardia and atrioventricular conduction abnormalities, and exaggerated pharmacological response in special groups (children, women, elderly) that may be related to single- or multiple-drug therapy.

◆ Impact of therapies designed to improve clinical outcomes
Spurred on by a high prevalence, mortality, and morbidity, research in heart failure has been extraordinary through the last 30 years. New pathophysiological mechanisms were identified and therapies with new drugs, devices, and management strategies have been tested with the aim to improve clinical outcomes in different clinical settings. Some trials demonstrated unequivocal benefit, including a reduction in mortality, while others had to be prematurely discontinued because of unacceptable secondary effects or unexpected increase in mortality. Nevertheless, all yield important information to better understand the disease. Overall, the concept, diagnosis, and management of heart failure have completely changed the prognosis and quality of life in patients with heart failure.

◆ Therapies associated with an improvement in outcomes in clinical trials
The first trial to demonstrate an improvement in survival was the CONSENSUS trial (COoperative North Scandinavian ENalapril SUrival Study), adding enalapril to the standard treatment of heart failure with digoxin and diuretics. This outstanding achievement changed the way physicians looked at heart failure: prognosis could be improved with medical therapy. Improving outcomes became a clear target in clinical practice and in the objectives of clinical research. After the CONSENSUS trial, many other trials with angiotensin-converting enzyme (ACE) inhibitors, including captopril, lisinopril, ramipril, and trandolapril, confirmed the benefit in different clinical settings, including asymptomatic left ventricular dysfunction and postinfarction heart failure. Since then, ACE inhibitors have become the cornerstone of heart failure with reduced left ventricular function.

Table III (left page). Desirable outcomes in heart failure clinical trials.

<table>
<thead>
<tr>
<th>Table III (left page). Desirable outcomes in heart failure clinical trials.</th>
</tr>
</thead>
<tbody>
<tr>
<td>First test stage parameters</td>
</tr>
<tr>
<td>▶ Safety</td>
</tr>
<tr>
<td>ABCD</td>
</tr>
<tr>
<td>ABCD</td>
</tr>
</tbody>
</table>

After accepting that medical treatment could dramatically change outcomes, the next huge change in the strategy of heart failure management came from the clear demonstration that β-blockers (contraindicated in heart failure due to the negative inotropic effect) further improve the outcomes. Carvedilol, metoprolol, bisoprolol, and to some extent bucindolol were clearly associated with a further improvement in outcomes when added to ACE inhibitors. The limitations of the use of β-blockers are derived from some side effects, in particular hypotension.
Angiotensin II receptor blockers (ARBs) were also extensively investigated, but without the success needed to dramatically change clinical practice; the role of ARBs is currently perceived as an alternative to ACE inhibitors. Aldosterone blockers, spironolactone, and eplerenone were the third group of drugs that demonstrated an extra benefit on top of ACE inhibitors and β-blockers and are now recommended in all patients without contraindication, mainly severe renal failure. Heart rate is directly related to heart failure outcomes and selective heart rate reduction with ivabradine, an If current inhibitor, further improves outcomes, introducing a new concept in the heart failure management strategy. The last achievement, yet to be implemented in clinical practice, comes from the PARADIGM-HF trial (Prospective comparison of Angiotensin Receptor–neprilysin inhibitor with ACE inhibitors to Determine Impact on Global Mortality and morbidity in Heart Failure). In this study, the new drug LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure, challenging the accepted paradigm of ACE inhibition as the cornerstone for heart failure treatment.

Table IV. Strategies with unequivocal evidence of major clinical outcomes improvement in patients with heart failure and reduced left ventricular ejection fraction.

<table>
<thead>
<tr>
<th>Medical therapy</th>
<th>Clinical setting</th>
<th>Improved outcomes</th>
<th>Year first evidence published</th>
<th>Limitations</th>
<th>Guideline recommendation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Systolic HF</td>
<td>Improved survival. Reduced rehospitalization.</td>
<td>1987</td>
<td>Hypotension, renal failure, hyperkalemia.</td>
<td>IA</td>
<td>1,2,18</td>
</tr>
<tr>
<td>ARBs</td>
<td>Systolic HF</td>
<td>Considered as alternative to ACE inhibitors. No extra reduction on mortality on top of ACE inhibitors.</td>
<td>2000</td>
<td>Hypotension, renal failure, hyperkalemia, in particular when associated with ACE inhibitors and aldosterone blockers.</td>
<td>IA</td>
<td>1,2</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>Systolic HF</td>
<td>Improved survival. Reduced rehospitalization. Reduced sudden death. Reduced reinfarction.</td>
<td>1999</td>
<td>Hypotension, bradycardia, asthma, AV block.</td>
<td>IA</td>
<td>1,2</td>
</tr>
<tr>
<td>Aldosterone blockers</td>
<td>Systolic HF</td>
<td>Improved survival. Reduced rehospitalization. Reduced sudden death.</td>
<td>1999</td>
<td>Renal failure, hyperkalemia.</td>
<td>IA</td>
<td>1,2</td>
</tr>
<tr>
<td>Hydralazine and nitrates</td>
<td>Systolic HF in selected ethnic groups</td>
<td>Improved survival. Reduced rehospitalization. Reduced sudden death.</td>
<td>2004</td>
<td>Benefit demonstrated in ethnic subgroups (African Americans).</td>
<td>IA</td>
<td>1,2</td>
</tr>
<tr>
<td>If inhibitors</td>
<td>Systolic HF, sinus rhythm and heart rate &gt;70 bpm</td>
<td>Improved heart failure survival. Reduced rehospitalization.</td>
<td>2011</td>
<td>Atrial fibrillation, bradycardia.</td>
<td>IB</td>
<td>1,2,14-17</td>
</tr>
<tr>
<td>Neprilisil</td>
<td></td>
<td>Improved survival. Reduced rehospitalization as compared with ACE inhibitors.</td>
<td>2014</td>
<td>Hypotension, renal failure, hyperkalemia.</td>
<td>Not approved yet.</td>
<td>19</td>
</tr>
</tbody>
</table>

**Devices**

| ICD             | Systolic HF | Reduced sudden death. | 1996 | Only applicable to selected patients. Does not slow progress of disease. | IA        | 1,2                   |
| CRT             | Systolic HF and LBBB | Improved survival. Reduced rehospitalization. | 2004 | Only applicable to selected patients (LBBB or QRS duration >160 ms). | IA        | 1,2                   |
| LV assist devices |               |                      |      |                                                      |           |                      |
| HeartMate       | Refractory HF, Selected patients | Improved survival. | 2004 | Only applicable to few, selected patients. Thrombosis. | 1,2       |                      |
| Heart transplant | Refractory HF, Selected patients | Admitted improved survival. No data from randomized trials. |      | Only applicable to few, selected patients. Organ rejection. | 1,2       |                      |

**Table IV.** Strategies with unequivocal evidence of major clinical outcomes improvement in patients with heart failure and reduced left ventricular ejection fraction.

*Abbreviations: ACE, angiotensin-converting enzyme; ald, aldosterone; AV, atrioventricular; bpm, beats per minute; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LV, left ventricular; ms, milliseconds.*

Based on references 1,2,14-19.
Somehow, diuretics should be included in this selected list of first-line medical therapies. There is not clear evidence of clinical benefit using diuretics in heart failure. Certainly, no major trial could demonstrate an improvement in outcomes and some large contemporary trials with new diuretic drugs were a failure, including vasopressin inhibitors (tolvaptan) and adenosine inhibitors (rolofylline).

**Failures of medical therapy in clinical research**

More often than not, clinical trials in heart failure fail to demonstrate the hypothesis and yield neutral results. This includes important groups of drugs with different mechanisms of action, including levosimendan,23 vasopressin inhibitors (tolvaptan),24 statins,25 new antiarrhythmic drugs (celivarone),26 darbepoietin,27 dihydropyridines and other calcium channel blockers,28,29 flosequinan,30 prostacyclins31 and endothelin antagonists.32-36

### Table V. Therapies with failure to demonstrate unequivocal evidence to improve outcomes in heart failure with reduced left ventricular ejection fraction. Based on references 1,2,23-57.

<table>
<thead>
<tr>
<th>Medical therapy</th>
<th>Clinical setting</th>
<th>Outcomes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotropes</td>
<td>Systolic HF</td>
<td>Increased mortality.</td>
<td>23,32-36</td>
</tr>
<tr>
<td>Xamoterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nesinaronine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoximone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pimobendan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibopamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levosimendan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td>Systolic HF</td>
<td>Increased mortality.</td>
<td>26,37-42</td>
</tr>
<tr>
<td>Flecaidine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dronedarone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celivarone</td>
<td>Systolic HF+ICD</td>
<td>Neutral; may increase arrhythmias.</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Systolic HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flosequinan</td>
<td>Systolic HF</td>
<td>Increased mortality.</td>
<td>43</td>
</tr>
<tr>
<td>Prostacyclins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>Systolic HF</td>
<td>Increased mortality.</td>
<td>44</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>Systolic HF</td>
<td>May increase mortality.</td>
<td>28,29</td>
</tr>
<tr>
<td>Mibefradil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelin antagonists</td>
<td>Systolic HF</td>
<td>May increase mortality and hospitalization. May induce hepatic toxicity and myocardial ischemia.</td>
<td>45-48</td>
</tr>
<tr>
<td>Bosentan, Tezosentan</td>
<td>Systolic HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressin inhibitors</td>
<td>Systolic HF</td>
<td>Neutral. Benefit in hyponatremia.</td>
<td>24</td>
</tr>
<tr>
<td>Tolvaptan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>Systolic HF</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darbepoietin</td>
<td>Systolic HF+anemia</td>
<td>Neutral. Increased thrombosis.</td>
<td>27</td>
</tr>
<tr>
<td>Nesiritide</td>
<td>Acute HF</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>Adenosine A1 blockers</td>
<td>Acute HF</td>
<td>Neutral. Increased stroke.</td>
<td>31</td>
</tr>
<tr>
<td>Rolofylline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inotropes</td>
<td>Acute HF</td>
<td>Increased mortality.</td>
<td>49-51</td>
</tr>
<tr>
<td>Dobutamine, Dopamine, Milrinone, Epinephrine</td>
<td>Acute HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inotropes</td>
<td>Acute HF</td>
<td></td>
<td>52,53</td>
</tr>
<tr>
<td>Milrinone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>HF, general</td>
<td>Reduction in hospitalization. Some benefit in selected subgroups.</td>
<td>54</td>
</tr>
<tr>
<td>Diuretics</td>
<td>HF, general</td>
<td>Improved symptoms. No evidence of improved outcomes.</td>
<td>1,2</td>
</tr>
<tr>
<td>ARBs</td>
<td>Diastolic HF</td>
<td></td>
<td>55</td>
</tr>
<tr>
<td>Irbesartan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Diastolic HF</td>
<td></td>
<td>56,57</td>
</tr>
<tr>
<td>Perindopril</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HF, heart failure; ICD, implantable cardioverter defibrillator.
nesiretide, adenosine inhibitors (rolofylline), and others. Furthermore, in many trials, new therapies were actually related to an increase in mortality, including inotropes (xamoterol, vesnarinone, enoximone, pimobendan, ibopamine), antiarrhythmic drugs (propafenone, sotalol, dronedarone), fluorosequinan, prostacyclins (epoprostenol), calcium antagonists (mibefradil), and endothelin antagonists. Table V (page 131) includes a list of therapies with neutral outcomes or negative results in clinical trials well designed to explore the effect of therapies on heart failure outcomes.

The reasons for these failures are not completely clear (Table VI) and do not necessarily indicate that the tested drug itself was the reason for failure.

Nonpharmacological therapies
Other management strategies have also demonstrated a significant clinical benefit, and have been included in the current recommendations in heart failure guidelines. Some may be applied universally; such is the case for exercise and team work in heart failure clinics. Others, such as implantable cardioverter defibrillators (ICDs), cardiac resynchronization therapy (CRT), and implantable ventricular assist devices should be reserved for very selected populations with specific characteristics.

Lessons learned
Through this extraordinary research journey 2 important lessons should be recognized:

– Heart failure outcomes may improve with a combination of strategies. Guideline recommendations should be followed.
– Well-defined hypotheses must be tested in outcomes trials before incorporating new treatments in clinical practice.

Future needs
New research
More research is needed as mortality and rehospitalizations remain a major problem in heart failure. New mechanisms of action and new drugs are currently being investigated and the results of ongoing clinical trials along with new management strategies and technology improvement of ventricular assist devices will provide further evidence to modify the landscape of heart failure outcomes.

Two clinical settings are of particular interest for future research: heart failure with preserved ventricular function and acutely decompensated heart failure where demonstrating evidence of benefit remains a challenge.

Guideline implementation
However, implementation of what we have learned so far is of paramount importance and following the guideline recommendations improves outcomes. Figure 2 simplifies the current guideline recommendation for medical therapy in heart failure patients.

Table VI. Reasons for failure in heart failure clinical trials.

<table>
<thead>
<tr>
<th>Reasons for failure in heart failure clinical trials</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor understanding of pathophysiology</td>
<td>Etiology. Animal models may not represent clinical heart failure. Genotype, racial differences.</td>
</tr>
<tr>
<td>Incomplete understanding of the drug</td>
<td>Secondary effects. Off-target effects. Comorbidities. Dose response not uniform in different populations (age, sex, etc).</td>
</tr>
<tr>
<td>Wrong selection of patients</td>
<td>Heterogeneous populations. Comorbidities. Nonresponders.</td>
</tr>
<tr>
<td>Diagnosis of heart failure uncertain</td>
<td>Diastolic dysfunction. LVEF and dyspnea not specific.</td>
</tr>
</tbody>
</table>

Figure 2. Indications for first-line medical treatment in patients with heart failure.

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BP, blood pressure; contraindication; Cr, creatinine; HR, heart rate; inh, inhibitors; K+, potassium ion; Na+, sodium ion; SR, sinus rhythm. Based on reference 59: Lopez et al. Diagnóstico y tratamiento de la insuficiencia cardíaca. iPad application. 2014. © CARDIOSESAMO.
Traditional components of efficacy measurement in clinical trials include mortality and hospitalization for cardiovascular reasons, but require a large number of patients to ensure the reliability of results. However, the size, duration, complexity, and costs associated with new, contemporary trials make clinical research ever more difficult and challenging. A more pragmatic approach simplifying the trials and maintaining relevant clinical outcome measures should be agreed upon between the scientific community and health care authorities.

References

1. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Eur Heart J. 2012;33:1787-1847.
THE VULNERABLE PHASE OF HEART FAILURE:
A WINDOW OF OPPORTUNITY

Keywords: heart failure; hospitalization; mortality; outcome

Le paysage changeant de l’évolution de l’insuffisance cardiaque

L’insuffisance cardiaque est une pathologie prévalente, létale et coûteuse. Depuis de nombreuses années, le traitement porte essentiellement sur l’amélioration des symptômes. La restriction sodée, les diurétiques, la digoxine et les dérivés nitrés étaient les principaux (et seuls) traitements employés pour soulager les symptômes et améliorer la capacité fonctionnelle. Puis l’étude CONSENSUS (COoperative North Scandinavian ENalapril Survival Study) a démontré que les médicaments pouvaient aussi prolonger la vie, ce qui a changé la pratique clinique et les objectifs de recherche dans l’insuffisance cardiaque. Depuis cette date, le traitement de première intention des patients insuffisants cardiaques comprend des β-bloquants, des antagonistes du récepteur de l’angiotensine 2, des antagonistes de l’aldostérone et des inhibiteurs du courant If, parallèlement à des traitements non médicaux comme les dérivatifs de la prostaglandine, la resynchronisation et d’autres stratégies thérapeutiques qui ont aussi démontré un bénéfice évident chez des populations sélectionnées. La recherche a été intensive et parsemée d’échecs. La plupart des principales études cliniques ont donné des résultats neutres ou même négatifs. Des études utilisant des médicaments inotropes ou antiarythmiques, des vasodilatateurs et d’autres médicaments ont dû être arrêtés prématurément à cause d’une augmentation inattendue de la mortalité. Le paysage du traitement de l’insuffisance cardiaque a néanmoins complètement changé. Des recommandations ont été préparées afin de conseiller des traitements basés sur les preuves pour améliorer la survie et réduire l’hospitalisation. La recherche continue, mais le défi imminent est de suivre les recommandations concernant les traitements qui prolongent la survie, réduisent l’hospitalisation et améliorent la fonction ventriculaire et la qualité de vie.

47. Packer M. Effects of the endothelin receptor antagonist bosentan on the morbidity and mortality in patients with chronic heart failure. Results of the ENABLE 1 and 2 trial program. Congress of the American College of Cardiology 2002; Late Breaking Clinical Trials: Special Topic #412.
Heart failure (HF) affects 2% of the total population, a prevalence that rises to over 10% in individuals aged over 65 years and is expected to increase continuously over the following years given the aging of the population. HF is the most common reason for hospital admission in the elderly. Hospitalization for HF (HHF) is associated with adverse prognosis with high in-hospital and postdischarge mortality as well as high postdischarge rehospitalization rates. At the same time, HF leads to a huge financial burden that accounts for 2% of the total health care expenditure for all medical conditions. The estimated total cost for HF in the United States in 2012 was $31 billion, and this amount is expected to rise to $70 billion in 2030. Approximately 70% of HF costs result from HHF, the main proportion of which represents ward costs. Interestingly, most of HF readmissions seem to be preventable as it is related to incomplete in-hospital therapy and a poor transition and follow-up plan. Thus, effective management of congestion, careful initiation and titration of evidence-based therapies, and proper planning of follow-up are the keys to prevention of HHF and thus reduction in the social and financial burden of HF.
Hospitalization for HF

Hospitalization for HF (HHF) represents the most common cause of hospital admission in the elderly [acute heart failure chapter], with a total of approximately 1 million admissions per year in the United States and a similar number in Europe.\(^3\) Hospital discharges with a diagnosis of HF clearly increased from 1980 to 2000.\(^3\) In the subsequent decade, 2000-2010, although hospitalizations with a primary diagnosis of HF declined, those with HF as a secondary diagnosis remained rather stable.\(^3\)

Hospitalization occurs commonly after the diagnosis of HF. In a population-based cohort, over a period of 5 years following the diagnosis of HF, 83% of patients were hospitalized at least once and 43% of them at least 4 times.\(^5\) The majority of patients hospitalized for HF have advanced age, usually above 70 years, and a previous history of HF as de novo HF represents less than one-third or one-fourth of cases.\(^7\) Left ventricular ejection fraction is preserved in approximately half of the patients, while the majority suffer from a wide range of cardiovascular and noncardiovascular comorbidities, including arterial hypertension, coronary artery disease, atrial fibrillation, diabetes mellitus, renal disease, chronic obstructive pulmonary disease, anemia, and depression. Comorbid conditions, particularly noncardiovascular ones, affect significantly the prognosis of the syndrome, represent a frequent cause of deterioration and readmission, and have a major impact on patients’ quality of life.\(^8\) The median duration of hospitalization ranges between 4 and 11 days.\(^7\)

Pooled data from a number of acute HF registries carried out in different parts of the world show that HHF carries an ominous prognosis.\(^8,15\) In-hospital mortality ranges between 4% and 7%. Following discharge, mortality rates during the first 2 to 3 months are as high as 7% to 11%, and reach 36% within a year after discharge. Postdischarge readmission rates are also high; about 25% to 30% of patients are rehospitalized during the first 2 to 3 months, while 66% are readmitted within a year. Interestingly, those high event rates do not differ between patients with reduced and preserved left ventricular ejection fraction, except for a higher in-hospital mortality rate observed in the former group.\(^16\) Postdischarge readmissions seem to follow a 3-phase pattern with an early peak during the first 2 to 3 months, followed by a prolonged plateau phase and a second late peak during the advanced and final stage.\(^15\)

The financial burden of hospitalization for HF

The cost of HF represents 2% of the total health care expenditure for all medical conditions.\(^16-18\) The estimated total cost for HF in the United States in 2012 was $30.7 billion, 68% of which was attributable to direct medical costs.\(^3\) As a result of the projected rise in the prevalence of the syndrome, this cost is expected to increase almost by 127% to $69.7 billion in 2030.\(^4\) The total health care expenditure that is attributable to HF, excluding the cost related to comorbidities, is expected to be 3-fold higher in 2030, summing a total of $160 billion.\(^4\)

The huge financial burden associated with HF results from recurrent admissions, multiple-drug therapy, widespread use of device and mechanical modalities—such as implantable cardioverter-defibrillators or ventricular assist devices—combined with prolongation of patients’ survival. Of all those components, the one that contributes the most to the total cost is hospital admissions. In the United Kingdom, the cost related to HHF in 1995 represented 69% of the total HF expenditure.\(^16\) The significance of the financial burden resulting from HHF is stressed by the recently introduced Hospital Readmission Reduction Program under President Obama’s Affordable Care Act (Sec. 3025), according to which hospitals with an excessive 30-day readmission rate of Medicare patients face penalties of up to 3% of their total Medicare reimbursement.

A study published in 2014 showed that the mean total cost per patient of an episode of HHF in a Greek tertiary/teaching hospital for a median hospital stay of 7 days reached €3200.\(^16\) This amount corresponded to hospitalization in the ward, laboratory investigations, and drug therapy, without taking into account several other costly procedures such as hospitalization in an intensive/cardiac care unit, cardiac catheterization, device implantation or other invasive diagnostic or therapeutic procedures, or the use of mechanical therapies such as circulatory support or renal replacement therapy that increase markedly the total expenditure. In an Irish teaching hospital, the mean cost of HHF (study published in 2000) was estimated to be £2146.\(^18\)

Ward costs appear to represent the greatest proportion of the total HHF cost, while medication contributes much less.\(^7,20\) In the aforementioned study from Greece, 79% of the total expenditure was attributed to ward costs, while laboratory investigations and medical treatment accounted for 17% and 4% of the cost, respectively.\(^16\) Similarly, in Ireland, ward costs represented 75% of the total HHF cost, while medications accounted for only 3.5%.\(^18\) Thus, the length of hospitalization is a key factor that determines the HHF costs.\(^20,22\) In addition, the expenditure seems to increase proportionally to the severity of the syndrome, as depicted by the New York Heart Association functional class, the extent of left ventricular systolic dysfunction, and the levels of natriuretic peptides upon admission, all of which represent independent predictors of the HHF cost.\(^17,18\)
In addition, the presence of comorbid conditions such as renal dysfunction also seems to affect the magnitude of the expenditure resulting from HHF.

Conclusions and key issues in preventing hospitalization-related HF burden

The increasing prevalence of HF, the constantly high HHF rates, the adverse prognosis associated with HHF, and the huge health care expenditure resulting from HHF are the main features that define the socioeconomic burden of HF. As HHF is the only major contributor to the total HF cost, the prevention of patients’ admission seems to be the key to reduction in costs and use of health care resources, and thus reduction in overall burden of the syndrome. It has been postulated that up to 75% of readmissions are preventable and related to incomplete in-hospital treatment—characterized by residual congestion and poor titration of chronic therapy—as well as to a poor transition and postdischarge follow-up plan. According to recent evidence from the European Society of Cardiology HF Long-term Registry, compliance with guidelines remains suboptimal not only in ambulatory, but also in hospitalized HF patients. Proper titration of life-saving HF medications, complete decongestion, treatment and prevention of exacerbating factors, education of patients, delineation of a specific follow-up plan, as well as collaboration with the patient’s attending physician are important measures that may contribute to a reduction in rehospitalization rates and thus help limit the socioeconomic burden of HHF.

References


4. Heidenreich PA, Albert NM, Allen LA, et al; American Heart Association Advo-
cacy Coordinating Committee; Council on Arteriosclerosis, Thrombosis and Vas-
cular Biology; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Stroke Coun-
cil. Forecasting the impact of heart failure in the United States: a policy state-


7. Fannakis D, Parissis J, Filippatos G. Acute heart failure: epidemiology, classi-

8. Fonarow GC, Abraham WT, Albert NM, et al; OPTIMIZE-HF Investigators and Hospitals. Factors identified as precipitating hospital admissions for heart fail-


10. Komajda M, Follath F, Swedberg K, et al. Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The Eu-
roHeart failure survey programme—a survey on the quality of care among pa-

11. Nieminen MS, Brutsaert D, Dickstein K, et al; on behalf of the EuroHeart Sur-
vvey Investigators. EuroHeart Failure Survey II (EHFS II): a survey on hospital-


15. Desai AS, Stevenson LW. Rehospitalization for heart failure: Predict or pre-


23. Maggioni AP, Anker SD, Dahlström U, et al; Heart Failure Association of the ESC. Are hospitalized or ambulatory patients with heart failure treated in ac-

Keywords: cost; expenditure; health care; heart failure; hospitalization
L’insuffisance cardiaque (IC) touche 2 % de la population totale, une prévalence qui s’élève à plus de 10 % chez les personnes âgées de plus de 65 ans et qui va augmenter constamment dans les futures années à cause du vieillissement de la population. L’IC est la raison la plus courante d’hospitalisation chez les personnes âgées. L’hospitalisation pour IC (HIC) s’associe à un mauvais pronostic, avec une forte mortalité hospitalière et post-hospitalière et à des taux élevés de réhospitalisation après la sortie de l’hôpital. En même temps, l’IC conduit à une énorme charge financière qui compte pour 2 % des dépenses totales des soins de santé pour toutes les pathologies médicales. Le coût total estimé pour l’IC aux États-Unis en 2012 était de 31 milliards de $, somme qui va atteindre 70 milliards de $ en 2030. Fait intéressant, la plupart des réhospitalisations pour IC semblent évitables, étant liées à un traitement hospitalier insuffisant et à un mauvais plan de transition et de suivi. Une prise en charge efficace de la congestion, une instauration et une augmentation soigneuses des doses des traitements basés sur les preuves ainsi qu’une planningification adéquate du suivi sont donc les clés de la prévention de l’HIC et donc de la diminution de la charge sociale et financière de l’IC.
Hospitalization of patients for heart failure is a landmark event in the clinical course of the disease. It reflects the prevalence of mechanisms causing fluid overload and/or lung congestion with symptoms of severe dyspnea and/or fatigue and need of urgent treatment and hospitalization. Despite relatively rapid relief of symptoms, hospitalizations for heart failure are followed by an increased risk of death and rehospitalizations. The mechanisms of these poor postdischarge outcomes are still incompletely understood and, to date, no treatment has improved such outcomes. Comorbidities, persistent congestion, and end-organ damage likely play a major role.

The prognosis of ambulatory patients with chronic heart failure and reduced ejection fraction (HFREF) has substantially improved in recent years with a decrease in hospitalizations and a slightly lower, though still significant, reduction in mortality.1-5 Annual mortality rates average 7%-8% for these patients. 4,5 However, heart failure (HF) remains a progressive disease and the rate of episodes of worsening HF is high, up to 20%-30% each year, in outpatients with chronic HF, 4,5 with an increased risk even in patients showing ejection fraction (EF) recovery. 6

Outcome rates after HF hospitalization
HF is the most important cause of hospitalization for subjects aged over 65 years and HF hospitalizations are a landmark event in the clinical course of the disease. Patients hospitalized for HF have an unacceptably high event rate, with up to 50% possibly having further events with a 10%-15% mortality rate and a 30%-40% rehospitalization rate within the first 6 months after discharge. 3,7,8 Unlike for acute coronary syndromes and chronic HFREF, there is as yet no evidence of efficacy for any new specific treatment for patients hospitalized for HF; thus no change in treatment and prognosis has occurred in recent decades.

In the recent ESC-HF pilot survey (European Society of Cardiology Heart Failure pilot) of the EURObservational Research Program, there were 2 patient groups: (i) ambulatory outpatients with chronic stable HF and (ii) patients hospitalized for acute HF. Patients with chronic HF had an annual all-cause mortality of 7.2% with an annual hospitalization rate of 31.9%. These rates increased to 17.4% and 43.9%, respectively, in the patients hospitalized for acute HF. 5 Similarly, the annual mortality rates of patients in the IN-HF survey (Italian Network on Heart Failure) were 5.9% in chronic outpatients with HF, and 19.2% and 27.7% in the patients hospitalized for either...
new-onset or chronic decompensated acute HF, respectively. Longitudinal prospective clinical trials have shown similar results. Compared with patients who remain in stable clinical condition, patients hospitalized for HF show a dramatic increase in their risk of dying and this is independent from baseline EF, with no difference between patients with HFREF and those with preserved EF (HFpEF). This risk of death decreases exponentially in the months following discharge, but remains three- to fourfold higher even 12-18 months after the initial hospitalization. HF hospitalizations are therefore associated with an increased risk of long-term death, and this effect on patient prognosis is similar to that described for acute coronary syndromes.

Thus, improving postdischarge outcome in HF patients remains a major unmet need of current clinical practice. A better understanding of the mechanisms underlying the poor prognosis of patients hospitalized for HF may help provide better care and improve postdischarge readmission and mortality.

Deaths and hospitalizations: is there a relation?
Rehospitalization and mortality are the most important outcomes in acute HF trials. However, they are not necessarily related. Early rehospitalizations 30 days after discharge are an important performance measurement for US hospitals. However, early rehospitalizations are poorly related to postdischarge mortality and an inverse relationship between 30-day rehospitalizations and mortality has even been shown. In the RELAX-AHF trial (RELAXin for the treatment of acute HF), serelaxin was associated with a lower numerical incidence of 60-day mortality and a higher 60-day rehospitalization rate. Whereas hospitalizations in patients with chronic HF are an index of HF severity and precede deaths, early postdischarge rehospitalizations may have a different meaning, as shown by their poor relation to mortality. Social support, patient adherence to treatment, and relief from congestion at the time of discharge may have a major role. Other factors influencing the early postdischarge rehospitalization rate are the length of the initial hospitalization—with an inverse relation in some, but not all, studies—and the volume of HF patients in the emergency department. An increase in body weight after discharge, a marker of congestion, has been associated with an increased risk of rehospitalization, but not of mortality.

Major influences on postdischarge outcomes in HF
Three major causes seem to affect postdischarge outcomes in HF patients: comorbidities, congestion, and end-organ damage, with the 2 latter causes likely related.

Comorbidities
Comorbidities, cardiovascular and noncardiovascular, have a major role in the postdischarge event rates of patients with HF. As they are, or seem, less likely to be influenced by HF treatment, they tend to be overlooked. Cardiovascular comorbidities that may precipitate rehospitalizations include myocardial ischemia, arrhythmias—namely atrial fibrillation—and uncontrolled hypertension. They are all tightly related to the clinical course of HF and may be potentially treated by targeted therapy at the time of first hospitalization.

The role of noncardiovascular comorbidities is extremely important, especially for rehospitalizations. In an analysis of the causes of rehospitalizations in US hospitals, the proportion of patients readmitted for the same condition was 35.2% after a first HF hospitalization. Thus, the majority of readmissions after a first HF hospitalization may not be due to HF itself.

In the EVEREST trial (Efficacy of Vasopressin antagonism in hEart failure: outcome Study with Tolvaptan), among the 4133 randomized patients, there were 5239 rehospitalizations and 1080 deaths during a median of 9.9 months. Of all the rehospitalizations, 39.2% were noncardiovascular, 46.3% were due to HF, and a minority due to stroke, myocardial infarction (MI), arrhythmia, or other cardiovascular causes. Of all deaths, 13.2% were due to noncardiovascular causes, 41.0% to HF, 26.0% to sudden cardiac death (SCD), and the rest to MI or stroke. Similar data were more recently obtained in the RELAX-AHF trial, with 19 of the 107 deaths (18%) due to noncardiovascular causes, 37 (35%) due to HF, 25 (23%) due to SCD, 15 (14%) due to other cardiovascular causes, and 11 (10%) classified as unknown.

Patients enrolled in controlled trials generally have a lower prevalence of comorbidities compared with those in the ”real world.” The impact of noncardiovascular causes of hospitalizations and death is therefore larger in observational studies. In the ESC-HF pilot survey, diabetes, chronic kidney disease, and anemia were independently associated with a higher risk of mortality and/or HF hospitalization. Other noncardiovascular comorbidities that may cause rehospitalizations include infections, chronic kidney dysfunction, and chronic pulmonary disease. Elevated blood glucose levels on admission and iron deficiency have also been shown to be independent prognostic factors in patients hospitalized for HF. In an analysis...
from the Cardiovascular Health Study of the risk factors for all-cause hospitalizations among elderly patients with a new diagnosis of HF, the only 2 cardiovascular variables related to outcomes were left ventricular EF and New York Heart Association (NYHA) class, whereas many noncardiovascular factors, namely diabetes mellitus, chronic kidney disease, weak grip strength, slow gait speed, and depression had prognostic value. As previously pointed out, many other noncardiovascular factors related to patient characteristics may affect early readmissions. These include lack of adherence to treatment, dietary indiscretion, drug and alcohol abuse, family and social support, and access to care.

**Congestion**

Congestion is the main cause of HF hospitalizations. Most HF hospitalizations are heralded by a gain in body weight and, when this does not occur because of prevailing fluid redistribution, other markers of congestion, such as pulmonary artery pressure or B-type natriuretic peptide (BNP) plasma levels are increased. Congestion also has a major role as a cause of postdischarge deaths and rehospitalizations.

Lack of, or slower, resolution of signs and symptoms of congestion during the first days of hospitalization for HF is associated with more adverse outcomes. In its most extreme form, lack of decongestion manifests in in-hospital worsening HF, and this event is an independent predictor of increased mortality. Clinical signs are poor surrogates of the hemodynamic status, and measurement of BNP levels may identify persistent congestion even in the presence of a seeming resolution of clinical signs. Lack of decrease in BNP levels during hospitalization is associated with poor prognosis. In the RELAX-AHF study, both worsening HF during the hospital stay and a lack of decrease in N-terminal proBNP (NT-proBNP) levels during hospitalization were associated with increased 180-day all-cause mortality.

Assessment of signs of congestion, such as pulmonary rales, jugular venous pressure, peripheral edema, and weight gain, is also important at the time of discharge or early after discharge. During hospitalization, better prognostic assessment can be obtained by other measurements, such as pulmonary artery pressure monitoring or, more simply, by BNP or NT-proBNP levels.

**Organ damage**

There are reasons to hypothesize that congestion is not the only determinant of the increase in cardiovascular events after discharge (Figure 1). Firstly, studies have shown that measurements related to congestion, such as weight gain, or poor diuretic response, are associated with rehospitalizations and short-term outcomes, but not with long-term mortality. Secondly, risk of death after a HF hospitalization remains increased in the long-term, up to at least 12-18 months after the event. This is consistent with persistent organ damage associated with the hospitalization, similar to what occurs after acute MI, rather than a mechanism more likely to cause symptoms, eg, congestion. Thirdly, in addition to BNP levels, other markers related to organ damage and/or function are independently related to outcomes, namely mortality, after a HF hospitalization.

The RELAX-AHF trial was particularly important with this respect, as biomarker measurements were repeated at baseline and during hospitalization and, differently from other cases, the study drug was not associated with untoward effects on outcomes. Changes in markers of myocardial damage (serum troponins), renal function (cystatin C), and liver function (transaminases) were shown to have an independent relation to 180-day mortality, which persisted after adjustment for their baseline values.

Multiple mechanisms may cause myocardial damage during acute HF. Consistently, an increase in plasma troponin levels is very common in patients hospitalized for HF and serum troponin levels are independent predictors of subsequent outcomes. In addition to baseline values and a rise in serum troponin levels during hospitalization, an index of an event-related myocardial necrosis, is a powerful predictor of outcomes. The relationship between chronic renal dysfunction and/or worsening renal function and poor outcomes in patients with...
HF is well established.\textsuperscript{40,53} However, there are important exceptions, as an increase in serum creatinine may have a neutral, or even favorable, significance when it occurs after intensive diuretic treatment or after the initiation of renin angiotensin inhibitors.\textsuperscript{53-56} Acute HF may cause kidney dysfunction through multiple mechanisms.\textsuperscript{53} More recently, the role of hepatic dysfunction has been shown. The increase in inferior vena cava pressure, caused by congestion, is transmitted backward causing cholestasis and death of the hepatocytes, shown by an increase in serum transaminases, and this has independent prognostic value.\textsuperscript{40,57}

Conclusions
Hospitalization is a landmark event in the clinical history of HF patients. It is caused by severe symptoms and their emergence is due to prevalence of the mechanisms causing fluid retention and congestion. Such an event is attended by other mechanisms, which in addition to the untoward effects of the hospitalization itself and to the effect of persistent congestion, cause organ damage with further deterioration of patient prognosis and increased mortality. This is the vicious cycle that new treatments for HF decompensation must try to interrupt.

References
3. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33:1787-1814.


**Keywords:** heart failure; outcomes; postdischarge; prognosis
Heart failure (HF) is a disease with high morbidity and mortality in the long run. Its course is not linear in nature, but characterized by spikes and nadirs with a changing risk profile. It also includes a period called the "vulnerable phase," during which the patient is at an increased risk for adverse outcomes. Here, vulnerability means that HF patients might experience unexpected outcomes, which could bring about windows of opportunity if addressed properly. This vulnerability is typically observed during the periacute HF period, which extends from initiation of an index acute HF event leading to admission, through a peridischarge period and up to 6 months after discharge. This vulnerable phase could potentially be divided into 3 overlapping phases. Of note, this relatively long-lasting phase is not based solely on a single pathophysiological mechanism, because HF is a complex syndrome. Hence, an individual, but collaborative, approach is required. Whatever the driving mechanisms, tailoring of an individualized therapy by a multidisciplinary team might provide patients with better outcomes and see them through to a stable phase of HF.

Medicographia. 2015;37:144-148 (see French abstract on page 148)
AHF is by nature a period of vulnerability. However, physicians can triage the patients according to disease severity and manage them accordingly, though referral to an intensive care unit (ICU)/critical care unit (CCU) itself means increased vulnerability. On the other hand, after an AHF episode, patients enter a vulnerable phase that can lead to repeated hospitalizations within a short period. This vulnerable phase requires accurate identification and management strategies.

With regard to risk prediction after discharge, several attempts to predict rehospitalization have been described in the literature. Most of these models performed poorly, though some of them may work in individual patients. The problem of poor performance might be related to the multidimensional nature of postdischarge management.

Typically, postdischarge adverse events peak up to 2 months after discharge, and then gradually decrease until reaching a plateau around month 6 of the postdischarge period. The plateau may last as long as a year, and then deteriorations may occur. Hence, the vulnerable phase of AHF could be considered to comprise 3 overlapping subphases (Figure 1): a very early phase, an early phase, and a late phase.

**Very early vulnerable phase**

The very early vulnerable phase is subdivided into further overlapping periods and so could be regarded as a heterogeneous period. It extends from an index episode of AHF up to a few days post discharge. As an episode of AHF itself is a vulnerable period, anyone experiencing one is subject to this vulnerability, which is characterized by increased risk of morbidity and mortality. Following an initial stabilization of an AHF episode, some patients, potentially up to 15% of the overall population, might experience worsening in HF symptoms and signs that require extra interventions. This has recently been introduced into the literature as “worsening HF.” In-hospital worsening of HF has been shown to be associated with an increased risk for adverse outcomes.

The very early vulnerable phase is typically expected in patients discharged before complete relief of congestion. The mean duration of hospitalization in the United States is 4-5 days. In many cases, this is too short for complete stabilization of the AHF patients. Overall, system-induced pressure encourages physicians to discharge patients as early as possible, which leads to the common practice in the United States (unlike many European countries) of using higher doses of diuretics within a short period of time to achieve decongestion.

High-dose diuretics might provide more rapid relief of symptoms and congestion, but at a slightly increased cost of renal impairment, and many patients would potentially remain relatively congested following such a discharge. Due to results of the rapidly changing tissue microenvironment, such as an electrolyte disturbance in the form of hypokalemia, tissue ischemia in the form of organ dysfunction may be overlooked at this stage. Of note, organ dysfunction, possibly in the form of renal or hepatic dysfunction, could determine the prognosis of these patients in the very early vulnerable phase. Furthermore, anemia at admission might contribute to poor outcomes in this phase if left untreated.

Long-term oral disease-modifying therapies are not easy to initiate within a short hospitalization period. Therefore, patients might experience increased risk of rehospitalization or fatality after discharge simply due to lack of administration of these therapies. These patients require meticulous follow-
The early vulnerable phase typically begins after the discharge of a relatively well-decongested patient following an episode of AHF. Hospitalization duration is typically 8-10 days in many European countries. That is usually a sufficient period for adequate decongestion and then stabilization of fluid balance (dry weight). However, that might not be long enough for adequate control of accompanying problems. PredischARGE, when possible, specialist HF nurses should be involved in educating the patient for nonpharmacological self-management of HF and for adjustment of diuretics in the outpatient setting. This would be helpful, as many of these patients require outpatient management of diuretics for some time. Early referral for cardiac rehabilitation should also be considered. These 2 factors—management of diuretics and cardiac rehabilitation—are important determinants of stability after AHF.

This phase of vulnerability is potentially secondary to a patient’s attitude, ie, restricting lifestyle modifications to the “honey-moon period” following discharge. However, most of the vulnerability is thought to be related to existing problems, ie, comorbidities. As many AHF patients also suffer from renal problems, anemia, hypertension, coronary artery disease, diabetes mellitus, or chronic obstructive pulmonary disease (though a cardiac problem could be relieved to an acceptable level), it is possible that accompanying problems will be uncovered with an index AHF event. These accompanying problems, which typically increase with age, might hold the patient in a period of risk beyond discharge. Therefore, each of the accompanying diseases is a potentially exacerbating factor and might require focused care unless well controlled. Patients with ischemic HF have been shown to be significantly more likely to experience repeated hospital admissions, and this theoretically means that repeated episodes of ischemia might be an important contributor to vulnerability. Elevated levels of biomarkers before discharge, such as natriuretic peptides and cardiac troponins, could potentially predict readmission risk. Hence, management during the vulnerable phase could be guided by biomarkers, though that remains to be firmly established.

Thirty percent of all readmissions occur within the first 2 months of hospital discharge. Furthermore, cardiovascular events are clustered before fatality. With a comprehensive plan and collaborative work, many of these events are preventable. Furthermore, overcoming the problem of systemic congestion does not mean relief of hemodynamic congestion in parallel. Patients in this phase might still require relatively higher doses of diuretics and vasoactive medications. They also require more careful and intimate follow-up. However, it has been shown that less than 50% of patients with HF with reduced ejection fraction (HFrEF) are prescribed guideline-recommended therapies at discharge.

Typically, β-blockers are recommended for most patients with chronic HF, although such therapy may be discontinued or reduced during hospitalizations. Long-term oral disease-modifying HF therapy should be continued on admission with AHF, except in the case of hemodynamic instability. It has been shown in severe, acutely decompensated HF patients that continuing the existing β-blocker therapy yields the best prognosis, while the worst belongs to those not prescribed β-blockers at discharge though they had been on long-term β-blocker therapy at admission. It has been demonstrated that such discontinuation is not needed in patients with AHF except in the case of cardiogenic shock. If heart rate remains elevated despite β-blockade in patients with HF, the addition of ivabradine would be beneficial. Additionally, in tachycardic AHF patients (in sinus rhythm) who cannot tolerate β-blockers, ivabradine remains an attractive option, though further studies are needed for this indication.

Prescription rates for these agents, namely, angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and mineralocorticoid receptor antagonists (MRAs), were all higher when patients were admitted to cardiology wards or seen by HF specialists. Furthermore, patients with HFrEF who were discharged along with a prescription for these drugs have significantly better outcomes than those discharged without. Notably, there is significant heterogeneity in the organization of HF management. Transition from inpatient to outpatient care can be very difficult in the vulnerable period due to the complexity of the progressive nature of the disease state itself, accompanying diseases and associated long-term medications, as well as the patient’s perception of the disease. Hence, collaborative care accounting for all variables is needed at every phase. Readmission rates for HF in younger adults are similar to those in elderly patients. Thus, a generalized risk after hospitalization is present regardless of age. Therefore, patients in this phase require closer clinical follow-up, typically within 1-2 weeks after discharge. Of note, a considerably high percentage of HF readmissions occur before the first scheduled ambulatory visit.

Late phase

The late phase typically extends up to 6 months. It is related to reactivation of the renin-angiotensin-aldosterone axis and the beginning of hemodynamic congestion before overt systemic congestion. Whatever the medical practice habits in different geographical areas, the overall prognosis of patients from different continents is similar in this phase. Independent of ejection fraction, HF-related rehospitalizations are typically preceded by a gradual rise in ventricular filling pressures more than 2 weeks before the appearance of the overt clin-
ical picture. Hence, a forthcoming episode should be thoroughly investigated according to symptoms and clinical signs, and using any existing modalities, including biomarkers. As AHF is mainly a condition of “congestion,” the accurate identification of signs of hemodynamic congestion is critical to the eventual prognosis of the patient.

Poor prognosis in the late phase could be prevented through fine-tuning (uptitration) of ACE inhibitors (or angiotensin receptor blockers), β-blockers, MRAs, and ivabradine. At this stage, medication adherence is also important to prognosis. Medication adherence should be achieved along with social support. Up to this late phase, adverse events decrease relatively over time and then reach a plateau, which could last several months. During this plateau, optimization of disease-modifying therapies, including device therapy should be the main target.

Conclusions
A vulnerable phase lasting up to 6 months following an episode of AHF exists and is a critical determinant of prognosis. In order to avoid the poor outcomes related to this vulnerable phase, patients should be discharged when they are hemodynamically stable for at least 24-48 hours, euvoletic, and managed on long-term oral medication, and when they have stable organ function, including the kidney and liver. It appears that the best management of the vulnerable phase requires a collaborative and multistep approach.

References

Keywords: acute heart failure; outcome; peridischarge; postdischarge; vulnerable phase

THE VULNERABLE PHASE OF HEART FAILURE: A WINDOW OF OPPORTUNITY

Definition and characteristics of the vulnerable phase in heart failure – Yilmaz and Mebazaa

MEDICOGRAPHIA, Vol 37, No. 2, 2015

147
L’insuffisance cardiaque (IC) est une maladie dont la morbidité et mortalité est élevée à long terme. Cependant, le cours de l’IC n’est pas linéaire de nature, mais caractérisé par des pics et des creux avec un profil de risque changeant. Cette évolution comprend aussi une période appelée « phase vulnérable », pendant laquelle le patient est à risque élevé d’événements indésirables. La vulnérabilité signifie ici que les patients IC peuvent avoir des suites inattendues, qui pourraient mettre en évidence des fenêtres d’opportunités si elles sont utilisées correctement. Cette vulnérabilité est généralement observée pendant la période péri-aiguë de l’IC, qui s’étend du début de l’événement d’IC aigu marquant conduisant à l’hospitalisation, jusqu’à une période entourant la sortie de l’hôpital et allant jusqu’à 6 mois après. Cette phase vulnérable peut éventuellement être divisée en trois phases qui se chevauchent. Il faut noter que cette phase relativement longue n’est pas seulement basée sur un mécanisme physiopathologique unique, car l’IC est un syndrome complexe. Il faut donc une stratégie individuelle mais collaborative. Quels que soient les mécanismes d’entraînement, l’adaptation d’un traitement individualisé par une équipe multidisciplinaire pourrait améliorer les suites des patients et les amener à une phase stable de l’IC.
Cardiac decompensation leading to hospital admission is a life-threatening condition, which always requires timely and accurate diagnostic and therapeutic procedures. Due to the clinical heterogeneity of patients with acute heart failure (AHF) and the complexity of underlying pathophysiology, a uniform and simple diagnostic and therapeutic algorithm does not exist. The entire in-hospital stay—from emergency department to hospital discharge—should always be viewed as a continuum, with clearly defined and prioritized therapeutic goals based on careful evaluation of the AHF patient’s clinical status. This paper will discuss the strategies that can be applied at each phase of in-hospital management in order to improve the outcomes of patients with AHF.

Immediate phase
During the initial (immediate) phase, beginning at admission, typically in the emergency department, major goals of management include:

(i) clinical stabilization (restoration of peripheral oxygenation and optimal ventilation, restoration of optimal hemodynamics and organ perfusion);
(ii) fast, effective, and sustainable relief of symptoms (most commonly dyspnea);
(iii) elimination of end-organ damage (including myocardium, kidneys, and liver);
(iv) reduction in the risk of early complications; and
(v) shortening of length of stay in intensive care.

Heterogeneity of patients with AHF
Difficulties in the management of HF decompensation are related to the complexity of this syndrome, owing to various, often unidentified, causes that include distinct clinical conditions with heterogeneous and often uncertain pathophysiology and the fact that its clinical course is modified by numerous cardiovascular and non-cardiovascular comorbidities. All these factors have significant effects on applied therapeutic strategies. It should be emphasized that there is no uniform and simple diagnostic and therapeutic algorithm for the management of patients with AHF.
Prompt treatment and careful monitoring
All patients admitted with AHF should be promptly treated, and diagnostic procedures should be implemented in parallel with respective treatment. Currently, therapeutic decisions are based on the initial presentation, clinical severity, and changes in clinical status, particularly in the initial phase. From the very beginning, monitoring of the patient’s vital functions is essential and many patients should be managed in an intensive or coronary care unit, at least during the initial hours.

Identification of life-threatening conditions
Firstly, the following life-threatening conditions should be identified and, if present, they should be adequately treated immediately:
(i) inadequate ventilation and/or peripheral oxygenation (treatment: oxygen; in more severe cases, noninvasive ventilation, or even endotracheal intubation and invasive ventilation);
(ii) life-threatening tachy- or bradyarrhythmias (treatment: electrical cardioversion or temporary pacing);
(iii) cardiogenic shock or symptomatic hypotension (treatment: inotropic agents and vasopressors; in more severe cases, mechanical circulatory support);
(iv) acute coronary syndrome as a potential cause of hemodynamic deterioration (treatment: coronary arteriography followed by revascularization); and
(v) acute mechanical cause as a potential cause of hemodynamic deterioration (treatment: imaging techniques followed by either surgical or percutaneous interventions).

Management of patients with AHF based on clinical profiles at admission
The clinical presentation of AHF ranges from a gradual worsening of chronic HF (ie, peripheral edema and dyspnea) to life-threatening pulmonary edema or cardiogenic shock. In clinical practice, a simultaneous assessment of congestion and peripheral hypoperfusion allows the identification of 4 different hemodynamic profiles,1,6 which predict outcomes, but most importantly pose several therapeutic consequences: (i) “wet and warm” (congestion and adequate peripheral perfusion; the most common clinical profile of AHF); (ii) “wet and cold” (congestion and peripheral hypoperfusion); (iii) “dry and cold” (no congestion and peripheral hypoperfusion); and (iv) “dry and warm” (no congestion and adequate peripheral perfusion).

Importantly, there are 2 distinct clinical entities within a “warm and wet” profile, which are triggered by different pathomechanisms and require different therapeutic strategies2,6:
(i) congestion due to fluid accumulation from concomitant weight gain and peripheral edema; typically, rather slow deterioration, gradual (over several days) development of symptoms, and a previous history of chronic HF with systolic dysfunction; treatment should be based on diuretics in order to remove fluid overload; and
(ii) congestion due to fluid redistribution from splanchnic circulation to the lungs without (or with minimal) weight gain; typically, rapid deterioration (sometimes flash pulmonary edema); treatment should be based on vasodilators, sometimes combined with rather low doses of diuretics.7,8,9

Diuretic strategies
Diuretics are the most frequently used drugs in patients with AHF. ESC guidelines recommend intravenous loop diuretics to reduce dyspnea and relieve congestion (class I, level of evidence B). Symptoms, urine output, renal function, and electrolytes should be carefully monitored to avoid hypovolemia, renal dysfunction, and hypokalemia.4 The optimal dose and mode of intravenous diuretic administration (bolus or continuous infusion) are uncertain, but in general, high doses may be deleterious. In patients admitted with pulmonary edema/congestion already taking loop diuretics, an initial dose should be 2.5 times the existing oral dose. In those with insufficient diuretic response, a switch from furosemide to bumetanide or torasemide or a combination of a loop diuretic and a thiazide (eg, bendroflumethiazide) may be considered after a careful assessment of fluid status. In selected cases, veno- nous isolated ultrafiltration can be used here. In patients with AHF and cardiorenal syndrome, a standard stepped pharmacologic-therapy algorithm has been shown to be superior to a strategy of ultrafiltration for the preservation of renal function, with a similar effect on weight loss with 2 approaches.10 Importantly, use of ultrafiltration has been associated with a higher rate of adverse events.

Vasodilating strategies
For patients with fluid redistribution and/or high systemic vascular resistance, a combination of vasodilator (the most commonly used are nitrates, but sometimes also nitroprusside or nitroglycerin) and diuretic should be used to relieve congestion and alleviate symptoms.4 They affect hemodynamics, ie, they reduce both a preload (and pulmonary capillary wedge pressure) and an afterload, and hence may increase cardiac output. Intravenous infusion of a vasodilator is recommended for

Selected abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>AHF</td>
<td>acute heart failure</td>
</tr>
<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>EVEREST</td>
<td>Efficacy of Vasopressin antagonism in hEart failuRE: outcome Study with Tolvaptan</td>
</tr>
<tr>
<td>HF</td>
<td>heart failure</td>
</tr>
<tr>
<td>ID</td>
<td>iron deficiency</td>
</tr>
<tr>
<td>SHIFT</td>
<td>Systolic Heart failure treatment with the I1 inhibitor ivabradine Trial</td>
</tr>
<tr>
<td>WRF</td>
<td>worsening renal function</td>
</tr>
</tbody>
</table>
patients with pulmonary edema/congestion and preserved systolic blood pressure (>110 mm Hg). Nitrate treatment may cause significant hypotension when administered without careful blood pressure monitoring, and a tolerance to prolonged nitrate use may occur. Nitrates should be used with caution in patients with concomitant, clinically relevant aortic or mitral stenosis. A recent study with nesiritide given in the early phase of AHF demonstrated only a modest symptomatic improvement without any impact on outcomes as compared with standard therapy.12

**Inotropic and vasopressor strategies**

In patients with low blood pressure, signs and symptoms of peripheral hypoperfusion, and low cardiac output, there is usually an indication to initiate inotropic support in order to stabilize compromised hemodynamics and improve peripheral perfusion.7 In clinical practice, therapy usually starts with dobutamine (a β1-adrenergic agonist producing dose-dependent positive inotropic and chronotropic effects), but phosphodiesterase III inhibitors (milrinone, enoximone) and levosimendan (calcium sensitizer improving cardiac contractility by binding to troponin C in cardiomyocytes) are also available. Dopamine is another often used inotropic agent, which stimulates β-adrenergic receptors (when used in moderate doses) and α-adrenergic receptors with subsequent vasconstriction (when used in larger doses, exceeding 5 μg/kg/min). If a combination of inotropic support and diuretic therapy is not leading to clinical stabilization, adding a vasopressor (mainly dopamine or norepinephrine) may be considered. In the most severe cases, intra-arterial blood pressure monitoring should also be considered; in some centers, pulmonary artery catheterization is applied in order to optimally treat severely compromised hemodynamics, which becomes the main goal of therapy. Another option that may be considered is temporary mechanical support with either an intra-aortic balloon pump or ventricular assist device, particularly if there are potentially reversible causes of acute deterioration (either as a bridge to a final decision or as a bridge to treatment response).

**Intermediate and predischarge phases**

Once clinical conditions are stabilized and there is symptomatic improvement, a patient is transferred to the ward where the next phases—intermediate and predischarge—are initiated.4,13,14 This period constitutes the initiation of the transition from hospital to ambulatory outpatient setting with relevant implications on the long-term outcomes. From the health care perspective, key recommendations should be initiated here, due to patient receptivity and the opportunity to implement long-term intervention strategies. In this phase, the following goals should be prioritized:

(i) maintenance of patient stabilization with optimized treatment;
(ii) initiation, up titration, and optimization of disease-modifying pharmacological therapy;
(iii) identification of the underlying HF etiology and relevant comorbidities;
(iv) careful consideration of device therapy in appropriate patients;
(v) optimization of fluid and hemodynamic status (targeting euvolemia);
(vi) predischarge risk stratification in order to identify high-risk patients; and
(vii) enrollment in a disease management program, education (regarding both a patient and relatives), and initiation of appropriate lifestyle adjustments.

Importantly, in addition to timely outlining of all these goals, in each phase of AHF, management should be adjusted to a patient's clinical profile and the effects of therapy carefully monitored. This strategy may result in further improvement of long-term outcomes.

**Management plan**

In all patients hospitalized due to AHF, after stabilization and transfer to the ward, a key element of effective management should be a detailed, individualized management plan, which should include the implementation of pharmacological interventions, devices, invasive procedures, and rehabilitation, obviously based on current recommendations.4 Most importantly, all medical professionals taking care of patients with AHF should have in mind that the major goal of applied therapies should not be just a reduction in mortality. Rather, they should make all available efforts to reduce the rate of subsequent HF hospitalizations, along with a reduction in days spent in hospitals, as well as to alleviate HF symptoms and to improve quality of life.

**Serial clinical monitoring**

An AHF patient transferred to the ward from the intensive care unit still needs careful clinical re-evaluation and monitoring. That should be based on simple, but clinically relevant, serial measures from physical examination, such as blood pressure, heart rate, body weight, severity of HF signs and symptoms (peripheral edema, pulmonary congestion, dyspnea, and jugular venous dilatation), along with basic laboratory tests (renal function, electrolytes). These clinical parameters on the one hand provide important prognostic information, but on the other hand, and most importantly, are crucial for further therapeutic decisions to be taken in patients with recent AHF. Recently, Metra et al15 proposed that predischarge assessment should be based on the comprehensive, but simple, evaluation of the following elements: clinical variables (signs of congestion, blood pressure, heart rate, and orthostatic test), electrocardiogram (duration of the QRS complex, presence of atrial fibrillation), and selected laboratory examinations (natriuretic peptides, renal function, electrolytes, anemia, iron deficiency [ID], and myocardial viability). Among them, elevated heart rate seems to be of particular interest as there is growing evidence that, similarly to chronic HF and also in patients discharged after HF decompensation, it predicts an unfavorable outcome.16,17 In a study of patients hospitalized for HF
with a left ventricular ejection fraction ≤40% and who are not in atrial fibrillation/flutter or pacemaker dependent (participants of the EVEREST trial [Efficacy of Vasopressin antagonism in heart failure: outcome Study with Tolvaptan], an increased heart rate ≥70 beats per min (bpm) in both 1- and 4-week postdischarge assessment was associated with increased all-cause mortality (Figure 1). In order to reverse this unfavorable phenomenon in such patients, it seems reasonable to consider pharmacological treatment to reduce resting heart rate during the early postdischarge phase using a β-blocker and/or ivabradine.

Optimization of pharmacotherapy
Based on clinical status, diuretic therapy should be optimized (a replacement of intravenous diuretics by oral diuretics, a reduction in daily diuretic dose to a minimal adequate dose, though still targeting euvoeoma). At the same time, in patients with systolic HF, life-saving therapies should be carefully implemented. These include angiotensin-converting enzyme (ACE) inhibitors (or angiotensin receptor blockers if ACE inhibitors are not tolerated), β-blockers, and mineralocorticoid receptor antagonists. Optimally, a triple combined therapy with these agents needs to be initiated in the hospital (based on clinical status and renal function permitting) and further optimized during the postdischarge period.

Revascularization and anti-arrhythmic strategies
In patients admitted with AHF, a potential ischemic trigger should always be taken into consideration. For those with co-incident of AHF with acute coronary syndrome, immediate transfer to a catheterization laboratory with further urgent revascularization should be considered. In all remaining patients, where on the basis of clinical evaluation myocardial ischemia can contribute to HF progression and hemodynamic decompensation, careful diagnostic procedures should be implemented; in the case of proven ischemia, an individualized decision about coronary revascularization with optimal mode and timing should always be discussed among the experts. It is also important to verify the indications for implantation of devices (implantable cardioverter defibrillator [ICD], cardiac resynchronization therapy [CRT]) as well as potential ablations of arrhythmias in patients with recent AHF.

Searching for comorbidities
According to the ESC guidelines, active screening for comorbidities and their optimal treatment is crucial for patients with HF and should constitute an element of a comprehensive assessment also during the intermediate and predischarge phases before the postdecompensation discharge. The presence of certain comorbidities, as well as their number, also contributes to the identification of particularly high-risk patients with recent AHF. Data from the Heart Failure Long-Term Registry demonstrate that the prevalence of most comorbidities is more common in patients hospitalized for worsening HF as compared with those with stable chronic HF (respectively for these 2 groups: atrial fibrillation, 44% vs 38%; diabetes mellitus, 39% vs 32%; chronic obstructive pulmonary disease (COPD), 20% vs 14%; prior stroke/transient ischemic attack (TIA), 13% vs 9%; renal dysfunction, 26% vs 18%; hepatic dysfunction, 8% vs 3%; all *P*<0.0001). Screening for comorbidities would allow identification of certain ones and to optimize their treatment, as well as to modify the standard therapies applied in patients with HF based on concomitant chronic diseases. Also, basic parameters such as ferritin or transferrin saturation, reflecting iron status

Figure 1. High resting heart rate during an early postdischarge period (1-week and 4-week) after hospitalization due to acute heart failure as a predictor of high mortality. Kaplan-Meier curves for all-cause mortality, by heart rate quartile. Log rank P<0.0001.

**Abbreviations:** bpm, beats per minute; EVEREST, Efficacy of Vasopressin antagonism in heart failure: outcome Study with Tolvaptan; HR, heart rate; Q, quartile.

After reference 16: Greene et al. JACC Heart Fail. 2013;1:488-496. © 2013, American College of Cardiology Foundation. Published by Elsevier, Inc. All rights reserved.
and recommended by ESC guidelines to be assessed in HF patients, allow diagnosis of ID and identify those who can be effectively supplemented. Of AHF patients, 37% have ID, which unfavorably affects their 12-month survival and could constitute a potential therapeutic target.

The prime example of a comorbidity that may affect the applied HF treatment is COPD. COPD, occurring in 20% of patients with recent AHF, worsens the prognosis and constitutes an important barrier to optimal β-blocker therapy and to an effective strategy for heart rate lowering (as COPD itself is accompanied by high resting heart rate). Data from the SHIFT trial (Systolic Heart failure treatment with the i Inhibitor ivabradine Trial) have shown that the primary composite end point of hospitalization for worsening HF or cardiovascular death, and its component, hospitalization for worsening HF, were more common in patients with COPD. β-Blockers were prescribed to 69% of COPD patients and 92% of non-COPD patients. The efficacy and safety profile regarding the ivabradine treatment were similar in patients both with and without COPD, hence this therapy could constitute an alternative to β-blockers as a safe and effective heart rate lowering strategy. Moreover, additional analyses from the SHIFT trial demonstrated that worsening renal function (WRF), a common problem in patients with recent AHF (defined here as a creatinine increase of ≥0.3 mg/dL and ≥25% from the baseline value), was directly proportionally related to baseline heart rate, with an incremental risk of 5% for every 5-bpm heart rate increment. WRF increased a risk of the primary composite end point of hospitalization for worsening HF or cardiovascular death and of all-cause mortality, whereas ivabradine therapy was equally safe and effective regarding a reduction in the primary composite end point in patients both with and without WRF. Similarly, recent evidence suggests that ivabradine therapy was equally safe and effective regarding a reduction in the primary composite end point in patients both with and without diabetes.

Plan for postdischarge management

The final (predischarge) stage of management of patients hospitalized due to AHF should comprise the analysis and synthesis of all data that were obtained during the hospitalization, including the clinical course during hospitalization, the applied therapeutic interventions and their effectiveness regarding the improvement in clinical status, and the comprehensive picture of cardiovascular and noncardiovascular status of the patient with its effect on therapeutic decisions. Taken together, this evidence should form the basis for the plan for further diagnostic and therapeutic steps during the postdischarge stage in the management of a patient discharged after circulatory decompensation. A beneficial plan would be the enrollment of a patient in a long-term outpatient disease management program, associated with proper education (regarding both a patient and his/her relatives), and an initiation of appropriate lifestyle adjustments, including a proper diet and exercise programs.

References

4. McMurray JJ, Adamopoulos S, Anker SD, et al; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology, Developed in collaboration with the Heart Failure Association (HFA) of the ESC, Eur. Heart J. 2012;33:1787-1847.

Keywords: acute heart failure; management plan; therapy optimization

OPTIMISATION DU TRAITEMENT CHEZ LES PATIENTS INSUFFISANTS CARDIAQUES ENTRE L’HOSPITALISATION ET LA SORTIE DE L’HÔPITAL

La décompensation cardiaque conduisant à l’hospitalisation est une pathologie potentiellement mortelle, qui nécessite toujours un diagnostic et des procédures thérapeutiques justes et dans les délais. Étant donné l’hétérogénéité clinique des patients en insuffisance cardiaque aiguë (ICA) et la complexité de la physiopathologie sous-jacente, il n’existe pas de diagnostic simple et uniforme ni d’algorithme thérapeutique. La totalité du séjour à l’hôpital, du service des urgences à la sortie de l’hôpital, devrait toujours être regardée comme un continuum, définissant et privilégiant clairement les buts thérapeutiques basés sur une évaluation claire de l’état clinique des patients en ICA. Cet article analysera les stratégies applicables à chaque phase de l’hospitalisation afin d’améliorer la survie des patients en ICA.
After discharge from hospital, patients with heart failure are at high risk of mortality and rehospitalization: around 20% of patients are readmitted within 30 days, and 5% may die during that period. In most countries, only a minority of patients gain access to multiprofessional disease management programs, which can provide early and repeated contact between the patient (and family) and the healthcare professional team. The evidence for improved outcome and experience of care of such an approach is robust. International guidelines clearly recommend this type of approach, with the most recent US guideline stating that a follow-up visit within 7 to 14 days and/or a telephone follow-up within 3 days of hospital discharge is "reasonable." The key components of a disease management program include optimized medical and device management, patient education, involvement in symptom monitoring and flexible diuretic dosing, follow-up after discharge, facilitated access to care during periods of decompensation, access to advanced treatment options, and the provision of psychosocial support to patients and the family/carers. A person-centered approach is essential to ensure optimal adherence to treatment and lifestyle changes. Technology can help support patient education, monitoring, and self-care. Increasingly, health care systems are aligning payment systems to improve heart failure care, particularly in the transition from hospital care to longer-term care in the community, but the room for improvement remains huge.

After discharge from hospital, patients with heart failure are at high risk of mortality and rehospitalization. In the most recently available data from England, 9.4% of patients died during the hospitalization, a further 6.1% died within 30 days of discharge, and readmission occurred in 19.1% by 30 days. In other European countries, reported rehospitalization rates are typically around 25% at 12 weeks. In the United States, 30-day readmission rates are similar: between 20% to 25%. Recurrence of heart failure is the single most common reason, accounting for 30% to 60% of all readmissions. More broadly, unscheduled contact with the health service after hospital discharge is greatest in the first few weeks and months, rising to 50% by 12 months. International guidelines recommend that patients undergo a clinical review by a clinician with experience in heart failure soon after discharge from hospital. The 2014 guideline from the National Institute for Health and Care Excellence (NICE) in...
England also recommends early clinical review.9 The goal is to provide a high-quality transition to outpatient and community care, supporting self-care where possible. Ideally, patients should be enrolled in a disease management program, but in the absence of such a structured multidisciplinary program, review by a clinician with experience in heart failure is considered better than "routine" follow-up in a general clinic or only in primary care.

The most recent US guideline suggests that it is reasonable for patients to have a telephone follow-up within 3 days of discharge and/or a face-to-face clinical review within 1 to 2 weeks (Table I).7,10-27 Data from several countries suggest that such early follow-up is the exception rather than the rule. In the United Kingdom only 56% of hospitalized patients have any follow-up organized with a multiprofessional heart failure team, and only 34% have such a follow-up within 2 weeks of discharge,1 and in France only 28% of patients visited their cardiologist within 3 months of discharge.28

**Content of disease management programs**

Heart failure–specific disease management programs are now standard in many high-income countries, at least for patients who are seen by cardiologists. They have evolved from nurse-led programs for drug titration and education, and have incorporated evidence from programs used to manage other chronic conditions, such as diabetes or asthma. The structure of the programs varies, but they usually start during the hospital admission and involve multiple follow-up visits either at the clinic or at home. The European Society of Cardiology (ESC) has published guidelines on such programs,8,29 with emphasis on several key components (Table II).3

The evidence for the benefit of such disease management programs is good, with reductions in rates of readmission and mortality, and improvements in quality of life compared with usual care.20-31 The nature of the interventions studied in randomized trials has varied, but most include inpatient contact and then early follow-up, often with telephone support in addition to face-to-face visits either in a clinic or at home.

However, the evidence base for such recommendations is largely confined to randomized trials from high-income countries. In a recent meta-analysis of disease management programs for heart failure, including 46 studies,32 30 (65%) were based in the United States or Canada, 9 in Europe, 6 in Australia or New Zealand, and only 1 came from a middle-income country, Argentina. More recently, a small randomized study of a nurse-based management program following discharge from hospital in Brazil reported an improved outcome for patients with heart failure, even for those with a low background level of education.33 The program consisted of up to 4 home visits of an hour’s duration after discharge from hospital. The first occurred within 10 days of discharge (in keeping with the most recent North American guidelines), and then at 1 month, 2 months, and 4 months after discharge. In addition, there were telephone calls during the program (4 calls of around 10 minutes) to reinforce the recommendations made during the home visits, to check the use of prescribed medication, and to answer questions about the condition and its treatment.
There may be an optimal amount of patient contact, particularly where the quality of “usual” care is high. In the COACH study (Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure), there was no improvement in patient outcome with an intensive support program provided by a nurse compared with either a moderate-intensity program or usual follow-up by a cardiologist.

Patient (and family) education is a key component of all disease management programs. The guideline of the Heart Failure Association of the ESC gives an extensive list of items that should be covered (Table III, page 158).

A person-centered approach

It can be easy to lose sight of the individual when running a disease management program: there can be a temptation to let “one size fit all,” and to “tick the boxes” rather than tailor the speed and approach to the patient and their family.

Health policy has increasingly signaled a move away from an emphasis on specific organs and disease, toward placing the “whole” person at the center of medicine. The health professional must try to understand what the illness means for the individual, within a social and psychological context. This necessitates listening to that particular person’s point of view, with the ultimate goal of sharing responsibility with them.

Clinicians should learn to ask not only “what is the matter?” but “what matters?” In other words, what are the patient’s interests, concerns, and fears about the specific conditions, symptoms, or treatment options? This moves us from the strictly biomedical view to a broader biopsychosocial and spiritual view, with power shared between the health care professional and the patient.

Clinical guidelines in cardiology are largely silent about the person-centered approach, other than to state or imply that the clinician must consider how best to apply the evidence base to their patient. In the guidelines for chronic conditions (such as heart failure), the multidisciplinary approach is strongly supported, with professionals working together (with the patient and family) in a coordinated manner. An explicit discussion of the person-centered approach is not given, but rather indicators of which “type” of patients might or might not benefit from specific interventions. This approach is still directive—the application of what the professionals consider the best treatment—without a fuller discussion of the issues on a more equal basis. Two key components of person-centered care are collaborative goal setting and action planning: agreeing on what, when, where, and how often specific actions are required and the barriers to such actions for that individual patient. Such an approach helps foster self-efficacy and may assist the person in moving from a position of dependence to that of being an “expert,” if that is what they wish.

The evidence that this can make a difference is emerging, and is likely to be something that politicians and society will increasingly expect of health care systems.

Self-care

Obviously, the individual with heart failure is key to the success of long-term management after hospitalization for this condition. Even with frequent contact with health care professionals, active involvement of the patient and their family or carers is important to optimize outcomes and the experience of care. Disease management programs aim to support self-care, where this is wished by the patient. There are 3 key components to self-care: maintenance, monitoring, and management. Maintenance involves adherence to medication and
life-style changes; monitoring includes keeping an eye on signs and symptoms of heart failure and activities such as daily weighing; and management implies making changes to therapy (such as diuretic dose) in response to a fluctuation in symptoms.

A large variation in adherence to self-management has been reported. In a global study, most patients reported taking their medication as prescribed, but adherence to exercise prescriptions was below 50%. Other studies report lower adherence to medication, even after hospital discharge, with

<table>
<thead>
<tr>
<th>Educational topic</th>
<th>Patient skills and self-care behaviors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition and etiology</td>
<td>• Understand the cause of heart failure and why symptoms occur</td>
</tr>
<tr>
<td>Prognosis</td>
<td>• Understand important prognostic factors and make realistic decisions</td>
</tr>
<tr>
<td>Symptom monitoring and self-care</td>
<td>• Monitor and recognize signs and symptoms</td>
</tr>
<tr>
<td></td>
<td>• Record daily weight and recognize rapid weight gain</td>
</tr>
<tr>
<td></td>
<td>• Know how and when to notify health care provider</td>
</tr>
<tr>
<td></td>
<td>• In the case of increasing dyspnea or edema or a sudden unexpected weight gain of &gt;2 kg in 3 days, patients may increase their diuretic dose and/or alert their health care team</td>
</tr>
<tr>
<td></td>
<td>• Use flexible diuretic therapy if appropriate and recommended after appropriate education and provision of detailed instructions</td>
</tr>
<tr>
<td>Pharmacological treatment</td>
<td>• Understand indications, dosing, and effects of drugs</td>
</tr>
<tr>
<td></td>
<td>• Recognize the common side effects of each drug prescribed</td>
</tr>
<tr>
<td>Adherence</td>
<td>• Understand the importance of following treatment recommendations and maintaining motivation to follow treatment plan</td>
</tr>
<tr>
<td></td>
<td>• Sodium restriction may help control the symptoms and signs of congestion in patients with symptomatic heart failure classes III and IV</td>
</tr>
<tr>
<td>Diet</td>
<td>• Avoid excessive fluid intake; fluid restriction of 1.5–2 L/day may be considered in patients with severe heart failure to relieve symptoms and congestion. Restriction of hypotonic fluids may improve hyponatraemia. Routine fluid restriction in all patients with mild to moderate symptoms is probably not of benefit. Weight-based fluid restriction (30 mL/kg body weight weight) 35 mL/kg if body weight &gt;85 kg may cause less thirst</td>
</tr>
<tr>
<td>Alcohol</td>
<td>• Moderate intake of alcohol: abstinence is recommended in patients with alcohol-induced cardiomyopathy. Otherwice, normal alcohol guidelines apply (2 units per day in men or 1 unit per day in women). 1 unit is 10 mL of pure alcohol (eg, 1 glass of wine, 1/2 pint of beer, 1 measure of spirit)</td>
</tr>
<tr>
<td>Smoking and drugs</td>
<td>• Stop smoking and/or taking illicit drugs</td>
</tr>
<tr>
<td>Exercise</td>
<td>• Understand the benefits of exercise</td>
</tr>
<tr>
<td></td>
<td>• Perform exercise training regularly</td>
</tr>
<tr>
<td></td>
<td>• Be reassured and comfortable about physical activity</td>
</tr>
<tr>
<td>Travel and leisure</td>
<td>• Prepare travel and leisure activities according to physical capacity</td>
</tr>
<tr>
<td></td>
<td>• When traveling, carry a written report of medical history and current medication regimen and carry extra medication. Monitor and adapt fluid intake particularly during flights and in hot climates. Beware adverse reactions to sun exposure with certain medications (eg, amiodarone)</td>
</tr>
<tr>
<td>Sexual activity</td>
<td>• Be reassured about engaging in sex and discuss problems with health care professionals. Stable patients can undertake normal sexual activity that does not provoke undue symptoms.</td>
</tr>
<tr>
<td>Immunization</td>
<td>• Receive immunization against influenza and pneumococcal disease according to local guidelines and practice</td>
</tr>
<tr>
<td>Sleep and breathing disorders</td>
<td>• Recognize preventive behavior such as reducing weight in obese patients, smoking cessation, and abstinence from alcohol</td>
</tr>
<tr>
<td>Psychosocial aspects</td>
<td>• Understand that depressive symptoms and cognitive dysfunction are common in patients with heart failure and the importance of social support</td>
</tr>
</tbody>
</table>

Table III. Essential topics that should be covered during patient education and the skills and self-care behaviors that should be taught in relation to these topics, according to the most recent European Society of Cardiology (ESC) guidelines.

adherence of only 80% at 1 month after discharge, and 60% to 65% between 3 months and 1 year after discharge.44 One survey suggested that a lack of understanding of discharge instructions and confusion engendered by conflicting instructions from the discharging physician and primary care physician were the main reasons for non-adherence to medication.45 Many patients continue to take previously prescribed medications, despite them being discontinued in hospital.46 In a recent US study, large variations in self-management were reported, even though individuals received self-care education at regular clinic visits.42 Only 9% of patients showed good adherence to 8 key behaviors—such patients had the lowest risk of hospital admission, days in hospital, and emergency room visits, and better health status (Figure 1).42

**Role of the family/carers**

Higher levels of social support from friends and family are associated with increased medication and dietary adherence.47,48 High levels of support from a partner are also important and improve self-care.49 Negative influence from family or friends is also possible,50 suggesting that health care professionals should work with the social network of patients where possible. Caring for a family member with heart failure can be a physical, emotional, and financial strain on carers.51,52 and many report a lack of social and emotional support and a lack of information and advice.53

**Who should be involved in postdischarge follow-up?**

Disease management programs are almost universally multiprofessional, and are typically coordinated by a heart failure nurse specialist. Evidence from observational datasets suggests that any clinical follow-up improves outcomes in heart failure, but there is incremental benefit from involvement of a multiprofessional team over that of either a primary care physician or a cardiologist alone.54 The core team may be small, but the skills of a wider range of health care professionals can be drawn upon when appropriate, such as a nutritionist, physiotherapist, occupational therapist, palliative care service, psychologist, or pharmacist.

**Remote monitoring**

In theory, remote monitoring of patients after discharge should allow remote decision making, facilitate patient self-care, and improve outcome after discharge from hospital. Although meta-analyses of small studies have suggested benefits on mortality and heart failure hospitalizations,55,56 large randomized trials have not confirmed such benefits.57,58 Many patients with heart failure have an implanted cardiac device, such as cardiac resynchronization therapy, and/or an implantable cardioverter defibrillator. Remote monitoring of such devices may, in some circumstances, improve the outcome for patients,59 although once again the evidence base is not consistent.60 Further studies are ongoing.61

Technology offers other opportunities to improve heart failure management by both professionals and patients. Interactive Internet-based education programs (such as heartfailurematers.org operated by the Heart Failure Association of the ESC), and patient support groups can provide useful material for patients and their families. Smartphone applications (“apps”) are also increasingly used to support lifestyle management, and may be useful in supporting rehabilitation. Online consultations (by Skype or other systems), e-mail communication, and transfer of data from home monitoring systems are changing the way patients and their families interact with their health care team. Concerns regarding legal liability, data confidentiality, and reimbursement are slowing implementation of these technological changes in many countries.62

**Palliative and end-of-life care**

Traditionally, cardiac services have not embraced a palliative care approach to end-of-life issues, although this has changed dramatically in recent years, particularly where multiprofessional disease management programs and teams are involved in care. In England, only 4% of heart failure patients were referred to palliative care services in 2012 after their admission, despite 6% of patients dying within 30 days of discharge, and 25% by 6 months.1 Palliative care takes a broad approach to disease management, addressing the physical, as well as psychological, social, and spiritual needs of patients and their families. Pain and symptom management are key elements of this approach and are most useful when introduced early on in the disease process so that patients and their families are famil-
iar with the concepts and services available as the needs arise. Organization and funding of palliative care services varies from country to country.

Patient surveys suggest that the majority of patients with heart failure do not feel that they have had an opportunity to adequately discuss end-of-life issues with their health care professionals, with unwillingness to tackle the subject found in both the patients and the health care team.23

Driving change

In a survey published in 2006, only 7 of 26 European countries reported that heart failure–management programs were being used in more than 30% of hospitals.24 Even when programs are in place, they are often underutilized. A survey in Canada showed that only 15% of patients hospitalized for heart failure were referred to a specialist clinic for follow-up.25

In France, a recent publication suggested that only 26% of patients were seen by a cardiologist within 12 weeks of discharge.26 and in the United Kingdom only 56% of patients were referred for heart failure follow-up at the time of discharge.7 In the United States, a Web-based survey reported wide variation in the implementation of key practices in a quality improvement initiative to reduce preventable readmissions after heart failure hospitalization: only 15% of hospitals employed all 4 recommended discharge and follow-up practices, and only 5% ensured all 3 classes of disease-modifying medication were in place.25

Health care systems have attempted to drive care toward multiprofessional and community care by a variety of means, including the introduction of “performance metrics.” Often, these relate to process measures, such as the use of various drugs or echocardiography, or evidence of delivery of education about smoking cessation or exercise advice. Readmission within 30 days is penalized in several countries, including the United States, Germany, and the United Kingdom. In the latter country, consideration is being given to the introduction of a “payment by results” tariff, so that reduced payment is made if certain procedures are not followed. There is good evidence that the adherence of clinical teams to guideline-recommended therapy is associated with better outcomes for patients. In the MAHLER survey (Medical mAnagement of chronic Heart failure in Europe and its Related costs), which was conducted in 6 European countries, after adjustment for potential confounding factors, patients that were seen by a clinical team that was highly compliant with guideline-based therapy had a 36% lower rate of cardiovascular rehospitalization over a 6-month period after discharge.65 Similar results have been reported more recently from Germany.66 Recent data from the national audit of heart failure admissions in the United Kingdom confirm that patients who see specialists, and those who are given more guideline-recommended therapy, have a better outcome after discharge from hospital.1 This has supported NICE to mandate universal access to such specialist input for patients admitted with heart failure to English hospitals from 2014 onward.9

Conclusions

The evidence base strongly supports the international guideline recommendations that heart failure patients should be followed-up by specialist services after discharge from hospital, ideally within the context of a multiprofessional disease management program. The highest risk period is in the first weeks to months after discharge, and input from the multiprofessional team during this period will help optimize the outcome and experience of care for the patient and their family/carers. A patient-centered approach is essential to ensure that support is tailored to the individual’s needs. Increasingly, health care systems are aligning payment mechanisms to incentivize best practice and better outcomes. Globally, the data suggest that there is considerable room for improvement—the majority of patients with heart failure who are admitted to hospital do not have access to good postdischarge follow-up and care, even in the wealthiest countries.

References

8. McMurray JJ, Adamopoulos S, Anker SD, et al; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33(14):1787-1847.

12. Fonarow GC, Heywood JT, Heidenreich PA, et al. Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: findings from Acute Decompensated Heart Failure National Regis-


15. Fonarow GC, Abraham WT, Albert NM, et al. Influence of a performance-improvement initiative on quality of care for patients hospitalized with heart fail-


17. Phillips CO, Wright SM, Kern DE, et al. Comprehensive discharge planning and postdischarge support for older patients with congestive heart failure: a meta-

18. O'Connor CM, Abraham WT, Albert NM, et al. Predictors of mortality after dis-


22. Windham BG, Bennett RG, Gottlieb S. Care management interventions for old-

23. Hernandez AF, Greiner MA, Fonarow GC, et al. Relationship between early exacer-


38. Ponsald AM, Heleer M, Choi HJ, Siever MJ, Pette JD. Family influences on self-


with the cardiology community. Eur Heart J. 2013;34:1864-1868.

63. Jaarsma T, Stromberg A, De Geest S, et al. Heart failure management pro-

64. Gravely S, Ginsburg L, Stewart DE, Mak S, Grace SL. Referral and use of heart

strategies for reducing 30-day readmissions: a national study. J Am Coll Car-

66. Komajda M, Lapuerta P, Hermans N, et al. Adherence to guidelines is a pre-
dictor of outcome in chronic heart failure: the MAHLER survey. Eur Heart J.

67. Frankenstein L, Remppis A, Fliegel A, et al. The association between long-
term longitudinal trends in guideline adherence and mortality in relation to age

**Keywords:** heart failure; hospitalization; postdischarge follow-up; postdischarge management

---

**ÉVALUATION ET PRISE EN CHARGE DES PATIENTS INSUFFISANTS CARDIAQUES APRÈS LEUR HOSPITALISATION**

Après la sortie de l’hôpital, les patients insuffisants cardiaques ont un risque élevé de mortalité et de réhospitalisation : environ 20 % des patients sont réhospitalisés dans les 30 jours et 5 % peuvent décéder pendant cette période. Dans la plupart des pays, seule une minorité de patients sont admis dans des programmes multiprofessionnels de prise en charge de la maladie offrant un contact précoce et répété entre le patient (et la famille) et l’équipe soignante. Il a été montré que cette approche améliore les résultats et la façon dont les patients vivent les soins. Les directives internationales recommandent clairement ce type de suivi : d’après les directives américaines internationales les plus récentes, une visite de suivi dans les 7 à 14 jours et/ou un suivi téléphonique dans les 3 jours suivant la sortie de l’hôpital sont « raisonnables ». Les points clés d’un programme de prise en charge de la maladie consistent en une optimisation de la gestion médicale et matérielle, une éducation des patients, une implication dans la surveillance des symptômes et un dosage flexible des diurétiques, un suivi après la sortie de l’hôpital, un accès aux soins facilité pendant les périodes de décompensation, un accès aux traitements de pointe et un soutien psychosocial aux patients et à leur famille ainsi qu’aux proches qui s’occupent d’eux. Une approche centrée sur la personne est essentielle pour une observance du traitement et des changements de style de vie optimaux. De son côté, la technologie peut faciliter l’éducation, le suivi et l’auto-prise en charge du patient. Les systèmes de santé tendent de plus en plus à mettre en place des systèmes de paiements coordonnés, afin d’améliorer le traitement de l’insuffisance cardiace, en particulier dans la transition des soins hospitaliers aux soins extrahospitaliers à plus long terme, mais des progrès importants restent à faire.
Heart failure has become a serious and expensive epidemic in the Western world, with hospitalization contributing to the greatest proportion of spending. Many strategies to improve quality of care can be implemented during or after hospitalization to ensure optimal outcomes and reduce readmission rates. In-hospital strategies include promoting the use of management protocols based on clinical practice guidelines and the use of checklists, as well as developing methods that deliver feedback to clinicians on care provided and outcomes. A variety of follow-up measures can be planned on hospital discharge. Patients who are seen early after hospitalization have better outcomes and fewer readmissions, and this benefit appears to be greater if the follow-up is carried out by a familiar physician and shared between the cardiologist and the primary care physician. Apart from the routine medical follow-up, other effective strategies include referral to day hospitals or heart failure clinics, structured telephone support, or telemonitoring of patient health status by way of different telemedical solutions, and last, but not least, patient empowerment through self-care activities that help them maintain physiological stability. All of the above can be effectively implemented through disease management programs aimed at improving the quality of care and patient outcomes while reducing health care expenditures.

Address for correspondence:
Prof José L. Zamorano,
Carretera de Colmenar Km 9.100,
28034 Madrid, Spain
(e-mail: zamorano@secardiologia.es)
www.medicographia.com
half within 18 months after discharge from hospital. In addition, in the United States, a recently launched collaborative tool that provides information on how well hospitals perform in all-kind quality-of-care–related statistical analysis shows that the national 30-day readmission rate for heart failure had limited improvement in recent years. A reduction in this carefully scrutinized hospital-performance–related parameter is a desirable objective, as it not only helps decrease the overall cost of medical care, but it also contributes to better quality of life for our patients.

Many strategies regarding quality of care could be implemented during hospitalization to improve care and ensure optimal patient outcomes (Figure 1), as it is well documented that a substantial proportion of patients admitted with heart failure receive less-than-optimal treatment, especially when they are hospitalized for other causes.

**In-hospital strategies**

**Management protocols**
A written, updated, and shared document that clinicians can consult when difficult decisions or clinical scenarios arise is desirable. Management protocols can be an initial step in improving quality of care in hospitalized patients, providing for standardized care and reducing undesired variation in clinical practice. Individual clinical expertise should only influence clinical management when scientific evidence is lacking or of insufficient quality.

These management protocols should be based on the best scientific evidence available, often found in clinical practice guidelines; it has been shown that their implementation results in significant improvement in outcome of care.

**Checklists**
Using something as simple and inexpensive as a checklist when patients are about to be discharged can greatly boost quality of care and decrease patient readmissions. A checklist can be of great help to attending physicians, as well as nurse practitioners and other house staff involved in patient care, reminding them about the convenience of applying various evidence-based pharmacologic (medications that should be prescribed or uptitrated during a patient’s stay, according to guidelines) and nonpharmacologic therapeutic measures (eg, the need to provide education, counseling, and follow-up instructions) (Figure 2).

Some studies have shown that the use of this kind of clinical tool can have a significant impact on improving quality of care by leading to a higher proportion of patients being treated with evidence-based therapies and correctly uptitrated drugs, which in turn leads to decreasing readmission rates and better clinical outcomes.

**Feedback**
A critical element for improving quality of care lies in providing clinicians with methods for monitoring care and outcomes of patients. Each facility should have a quality assessment and improvement program specific for heart failure where the extent to which clinicians practice in accordance with clinical guidelines can be assessed. The most powerful method appears to be the sharing of feedback on data comparing clinicians with their colleagues and education carried out at the local level by respected fellows.

A prospective registry, whether local or national, can be a useful tool. By collecting patient characteristics and performance measures during hospitalization and capturing postdischarge outcomes during follow-up, clinicians can receive feedback on their adherence to evidence-based guideline recommendations and quality of care provided.

Several national and local initiatives have been undertaken in this field using a variety of mechanisms, including national tracking and reporting of quality indicators through health plan claims and reviews of medical records. These initiatives provide feedback to practitioners on quality indicator adherence through peer review, require hospitals to submit performance measure data, and provide performance-improvement tools to enhance adherence.

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
</tbody>
</table>

Figure 1. Schematic showing various in-hospital and postdischarge follow-up strategies to ensure optimal patient outcomes.
### Heart Failure Checklist

**Cardiologist/physician:**

**Admission date:**

**Discharge date:**

---

<table>
<thead>
<tr>
<th>Medications prescribed (home)</th>
<th>Yes</th>
<th>No</th>
<th>↑</th>
<th>↓</th>
<th>Dose</th>
<th>Reason or comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor/ARB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other antiaggregant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acenocoumarol/Warfarin/NOAC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid-lowering agent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Yes</th>
<th>No</th>
<th>Reason or comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular risk assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking cessation counseling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dietary and physical activity education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment and adherence education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure/monitoring education</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Date</th>
<th>Reason or comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiologist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary care physician</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac rehabilitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral anticoagulant control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Date of completion:**

**Signature:**

---

*Figure 2. Example of a simple, inexpensive heart failure checklist, which can have a significant impact on patient quality of care.*
Hospital discharge and follow-up strategies

◆ Early follow-up
The days following discharge are a vulnerable period for patients suffering from heart failure because of their advanced age, the presence of comorbid conditions that could hinder the complete resolution of episodes of decompensation (e.g., chronic kidney disease), the complexity of pharmacological regimens employed, and the great number of physicians who may be involved in their subsequent care. It is usually necessary to rely on new medical therapies or to make changes in previous ones that could worsen their clinical condition, cause secondary effects, or even destabilize other comorbidities. In a retrospective cohort study conducted in Canada involving patients discharged from acute care hospitals with the diagnosis of new-onset congestive heart failure, those who received a regular cardiovascular follow-up had fewer visits to the emergency department (38% vs 80%; \( P < 0.001 \)), fewer admissions to hospital (13% vs 94%; \( P < 0.001 \)), and showed a lower 1-year mortality (22% vs 37%; \( P < 0.001 \)) compared with those with no follow-up visit.\(^\text{15}\)

Although aftercare tracking on a 6-monthly basis may seem adequate for patients with stable disease, current guidelines recommend an early follow-up after certain circumstances, such as a recent hospital admission,\(^\text{16}\) given that prompt follow-up of patients hospitalized for heart failure has been associated with lower rates of death and readmission. In a study carried out in 225 hospitals in the United States among Medicare beneficiaries hospitalized for heart failure, patients discharged from centers with a greater proportion of early follow-up (defined as an outpatient evaluation visit with a physician within 7 days after discharge) had lower rates of all-cause 30-day readmissions.\(^\text{17}\)

◆ Physician continuity
Physician continuity has been demonstrated to positively influence postdischarge outcomes beyond the sole effect of an early follow-up. In a recently published observational study conducted in Canada regarding risk of death or urgent all-cause readmission over 6 months in 24,373 patients discharged from hospital with a first-time diagnosis of heart failure, patients who had follow-up visits with a familiar physician (defined as one who had seen the patient at least once during the index admission or at least twice in the year before the index admission) had a lower risk of death or unplanned readmission (hazard ratio [HR] 0.91; 95% confidence interval [CI], 0.85-0.98) than those followed by an unfamiliar physician, whether specialist or not.\(^\text{18}\) Moreover, another observational study revealed that the benefit is not limited to patients discharged from hospitalization, but has also been observed to extend to patients treated and released from emergency departments, a population known to have worse 30-day outcomes than those actually admitted.\(^\text{19}\) In a cohort of 12,285 patients treated and released directly from various emergency departments in Canada, the risk of death or hospitalization was lower in patients followed by a familiar physician compared with those followed by an unfamiliar physician, at 3 months (HR 0.79; 95% CI, 0.71-0.89) as well as at 12 months (HR 0.87; 95% CI, 0.80-0.96).\(^\text{20}\) The previous observations raise the question of whether we could be achieving suboptimal outcomes by sacrificing physician continuity in order to meet early follow-up deadlines.

◆ Collaborative care
Although many patients suffering from heart failure receive care only by a primary care physician, being the gatekeeper of referrals to specialist care, a lot of patients in the postemergency setting (that is, after discharge from hospital or after visiting the emergency department) are only seen by a cardiologist. However, patients who receive concurrent care by both a primary care physician and a specialist within 30 days from discharge showed a lower rate of death at 1 year (7.2%) compared with those who only visited a primary care physician (10.4%; \( P < 0.001 \)). Moreover, patients with shared care had the highest rates of left ventricular ejection fraction evaluation, noninvasive testing for ischemia detection, and cardiac catheterization.\(^\text{21}\)

Some studies suggest that collaborative care entails a trade-off between lower mortality and higher rates of hospitalization,\(^\text{15}\) whereas others found no impact of specialist care.

◆ Day hospitals
Day hospitals allow evaluation and management of mild to moderate decompensations by short therapeutic interventions, arising as an efficient alternative in maintaining continuity of care while preventing readmissions, improving accessibility, increasing patient comfort, and reducing costs. Compared with other strategies, day hospitals or heart failure clinic-based disease management models can deliver more options in diagnostic tools and equipment, facilitating acute care.\(^\text{22}\)

In a study aimed at assessing and comparing the effectiveness and cost utility between a heart failure management program delivered by day hospital or usual care, patients referred to one of these facilities (with a staff consisting of a cardiologist, 4 trained nurses, and 2 physiotherapists, as well as other part-time collaborators)—where a series of interventions including cardiovascular risk stratification, correction of causes of instability, and continuous optimization of therapy could be applied—showed better results in management outcomes as well as in hard outcomes. A smaller percentage of patients referred to day hospitals experienced readmission compared with patients in the usual care group (8% vs 35%; \( P < 0.05 \)) or suffered cardiac death (2.7% vs 17.2%; \( P < 0.05 \)). This model also showed a better cost-utility ratio than community management.\(^\text{23}\)
Structured telephone support
It is feasible to educate, monitor, and give support to patients through self-management programs after discharge using simple telephone technology in a structured format. Through a series of scheduled calls with a specific goal and thoughtful questioning, a clinician can assess medication adherence, input-output balance, abrupt changes in body weight, and the convenience of medication adjustment, among other things. Although 2 large meta-analyses of randomized clinical trials—1 meta-analysis focusing on telemonitoring and structured telephone support and the other covering a broader range of transitional care interventions—showed a reduction in congestive heart failure–related hospitalizations and a trend toward reduction in all-cause mortality, this did not correlate with a reduction in all-cause hospitalizations. Furthermore, individual randomized clinical trials showed mixed results. Therefore, the available evidence is insufficient to support a clear recommendation.

Compared with other strategies, telephone-support disease management models are low cost and time efficient, and have been shown to be convenient for both the team and the patient. Nevertheless, it can be difficult to objectively assess symptoms and signs of heart failure by this strategy and implementation of large adjustments in treatment can be challenging.

Remote monitoring or telemedicine
Advances in telecommunication technologies have made possible the continuous care of patients at any place as an adjuvant to standard care, while contributing to the self-empowerment of patients. Through different telemedical solutions, some of them based on the use of implantable devices, selected physiological measurements can be collected and analyzed to ensure an early detection of disease deterioration, prompting medical intervention. The key to the effectiveness of telemedical management hence relies on the predictive value of the chosen monitored variables.

As a noninvasive approach, body weight monitoring has been considered for many years the cornerstone in traditional telemedicine. Although it may seem a simple measurement at first glance, there are several shortcomings due to body weight being easily influenced by clinical status or changes in food or fluid intake. It is also possible to assess parameters such as oxygen saturation, body impedance, and physical activity. Other monitoring strategies involve special drug containers that are able to send a signal when opened, thus helping assess adherence.

Minimally invasive approaches include measurement of serum concentrations of certain biomarkers, such as blood glucose or brain natriuretic peptide, or utilization of already in-use devices, like implantable cardioverter defibrillators or pacemakers, to monitor device function and usage or even some physiological variables, such as heart rate or type of rhythm. More invasive approaches include the insertion of implantable devices specifically designed with telemonitoring purposes. Some of these tools, such as a wireless pulmonary artery hemodynamics monitoring system, have been shown to reduce hospitalizations, although data on efficacy in improving outcomes is still lacking.

Self-care promotion
Self-care promotion, defined as the encouragement of “a naturalistic decision-making process that patients use in the choice of behaviors that maintain physiological stability and the response to symptoms when they occur,” can be a very convenient ally for clinicians.

In a systematic review of randomized trials of multidisciplinary management programs in heart failure, those aimed at enhancing patient self-care activities effectively reduced heart failure–related hospitalizations (relative risk [RR] 0.66; 95% CI, 0.52–0.83) and all-cause hospitalizations (RR 0.73; 95% CI, 0.57–0.93), without achieving an effect on mortality. The interventions led in the publications analyzed included nurse-delivered patient education, mailed patient education materials, home visits after discharge to reinforce education and self-care, or regular telephone contact by a nurse educator to monitor for deterioration. Similarly, on another systematic review of randomized clinical trials focusing specifically on self-management interventions in which patients retained the primary role in managing their health condition (which included education sessions or educational software providing information about signs and symptoms of heart failure, importance of daily weighing, dietary restrictions, and importance of adherence to the medication prescribed), self-care activities reduced heart failure–related readmissions (odds ratio [OR], 0.44; 95% CI, 0.27–0.71) and all-cause hospital readmissions (OR 0.59; 95% CI, 0.44–0.80).

Moreover, some studies show that self-care measures may provide a benefit in terms of reduction in risk of death. In a randomized controlled trial comparing a self-management program (consisting of a 1-hour educational session in which patients were given an educational booklet designed for low-literacy patients and a digital scale, a personalized management plan centered on the patient’s ideal weight and modifications in dosage of diuretic medications, and scheduled follow-up phone calls) with usual care among outpatients with a diagnosis of heart failure, the intervention group had a lower rate of hospitalization or death (adjusted incident rate ratio [IRR] 0.52; 95% CI, 0.32–0.89).

Toward the era of integrated care and disease management programs
All of the above quality-of-care strategies have been accepted to be useful tools that by themselves can have an impact on patient outcomes, but this raises questions about which
one would provide better outcomes, or to which one we should pool our efforts. Disease management programs have emerged in the past decade as a potential strategy to enhance the quality of care received by patients suffering from chronic conditions by bringing together some of the above components. It can not only increase the quality of care, the adherence to guidelines and care protocols, and the access to health services, but it can also be an effective way of improving the efficiency of health care services delivery by maintaining or improving quality while reducing costs.

Evidence regarding the characteristics and effectiveness of various interventions often used in disease management programs has been published. Provider-centered components, such as education and feedback, all of which can help to increase adherence to guidelines, as well as patient-centered components, such as reminders and financial incentives, have been associated with improvements in patient disease control. Furthermore, a meta-analysis including 11 randomized clinical trials showed that disease management programs were cost effective and patients cared for by these programs were more likely to undergo fewer hospitalizations.

The American Heart Association recommends a series of principles for guiding the development, implementation, and evaluation of disease management strategies. First, the main goal of disease management should be to improve the quality of care and patient outcomes, and should not be solely based on their efficacy in reducing health care expenditures. Second, these programs should be founded on scientifically based guidelines, focusing on encouraging patients and caregivers to follow treatment plans based on the best available evidence. Third, scientifically derived evaluations and consensus-driven performance measures should be included as a crucial component of any disease management program, to maximize benefit and facilitate its own refinement. Fourth, these strategies should support and enhance the patient-provider relationship within an integrated and comprehensive system of care. And lastly, these programs should address potential handicaps, which include the complexity of medical comorbidities, the challenges of the underserved and vulnerable populations, and the potential conflicts of interest of the organizations involved.

A related and often inadvertently overlooked tool for improving quality of care and patient outcomes lies in providing our health professionals with the best available information on how to do so. In this regard, continuing medical education and promotional education programs can help us maintain competence and learn about old and new strategies in the developing field of quality of care. Some studies suggest that these kinds of activities can help improve physician performance, especially in resource utilization, counseling strategies, and preventive medicine, and can have a positive impact on patient health care outcomes.

Although these programs are promising, there is a need for testing and demonstrating best practices and for sharing information on successful components across a wide range of scenarios and a variety of care settings.

References

21. Lee DS, Stukel TA, Austin PC, et al. Improved outcomes with early collabora-
tive care of ambulatory heart failure patients discharged from the emergency
22. Jaarsma T, Strömberg A. Heart failure clinics are still useful (more than ever?).
comparison between heart failure management program delivered by day-hos-
24. Inglis SC, Clark RA, McAlistier FA, Stewart S, Celand JG. Which components
of heart failure programmes are effective? A systematic review and meta-analy-
sis of the outcomes of structured telephone support or telemonitoring as the pri-
mary component of chronic heart failure management in 3832 patients: Abridged
25. Feltner C, Jones CD, Cené CW, et al. Transitional care interventions to prevent
readmissions for persons with heart failure: a systematic review and meta-anal-
in persons with heart failure: a scientific statement from the American Heart
27. Riegel B, Moser DK, Anker SD, et al. State of the science promoting self-care
in persons with heart failure: a scientific statement from the American Heart
disease management: principles and recommendations from the American
Heart Association’s Expert Panel on Disease Management. Circulation. 2004;

**Keywords:** heart failure, hospitalization, readmission, mortality, quality of care

---

**IMPACT DES INITIATIVES D’AMÉLIORATION DE LA QUALITÉ DES SOINS
CHEZ LES PATIENTS HOSPITALISÉS POUR INSUFFISANCE CARDIAQUE**

En Occident, l’insuffisance cardiaque prend la forme d’une épidémie sévère aux coûts importants générés en ma-
jeure partie par l’hospitalisation. De nombreuses techniques d’amélioration de la qualité des soins peuvent être mises
en œuvre pendant ou après l’hospitalisation pour optimiser les résultats et diminuer les taux de réadmission. Au sein
de l’hôpital, les stratégies utilisées sont des protocoles de prise en charge basés sur les recommandations de pra-
tique clinique, l’utilisation de listes de points à vérifier ainsi que des méthodes en cours d’élaboration sur le retour
d’information fait aux médecins au sujet des soins délivrés et des résultats. À la sortie de l’hôpital, plusieurs mesures
de suivi peuvent être prévues. Les patients qui sont vus précocement après l’hospitalisation ont de meilleurs résul-
tats et sont moins réhospitalisés, d’autant moins si le suivi est fait par un médecin connu et partagé entre le cardio-
logue et le médecin traitant. À côté du suivi médical de routine, d’autres méthodes efficaces comprennent l’ori-
tention vers l’hôpital de jour ou les établissements spécialisés pour insuffisants cardiaques, le soutien téléphonique
structuré ou la télésurveillance de l’état de santé du patient par le biais de la télémédecine sous différentes formes
et enfin, mais non des moindres, la responsabilisation du patient par des activités auto-thérapeutiques qui aident
au maintien d’une stabilité physiologique. Toutes ces méthodes peuvent être mises en place au sein de programmes
de prise en charge de la maladie dont le but est d’améliorer la qualité des soins et le suivi des patients tout en di-
minuant les dépenses de santé.
This fellowship is designed to foster the work of young researchers in the cardiovascular field

Who may apply?

Eligibility: applicants should be 35 years of age or less, PhD or equivalent graduation within the last 3 years, and ISHR-ES members at the time of the application deadline, March 31, 2015. The planned research project is to be completed within one year and should be presented at the ISHR European Section Annual Congress in 2016.

What is the ISHR-ES/SERVIER Research Fellowship?

A €20,000 grant is offered by SERVIER in partnership with the European Section of the ISHR to support a cardiovascular research project within a European research group for a period of up to 1 year.

How to apply

Send a PDF file containing the following information:

- Curriculum vitae
- List of publications
- A description of your research proposal as a 1-page summary + no more than 6 pages of text
- One letter of support from a supervisor

to David Eisner
eisner@manchester.ac.uk
as well as a copy to jenny.parr@manchester.ac.uk

Receipt of all applications will be acknowledged.

Please refer to instructions and templates on the ISHR Web site:
www.ishr-europe.org

DEADLINE FOR APPLICATIONS
March 31, 2015
Servier promotes in-depth understanding of the current body of knowledge on a specific area of cardiovascular medicine through sponsorship of the following grants:

- The Servier Research Grant in Hypertension of €30,000 is awarded every 2 years for a research proposal in the field of hypertension and related diseases with a focus on end-organ damage, surrogate markers, and biomarkers.

- The committee of the Servier Research Grant in Hypertension is composed of internationally renowned experts in hypertension and related cardiovascular diseases. The winner will receive the grant from the President of the ESH, during the award ceremony of the ESH Congress.

- This initiative follows the Servier SNS Research Grant, awarded from 2003 through 2007. The winners were Markus Schlaich, Krzysztof Markiewicz, and Gino Seravalle.

- The winners of the Servier Research Grant in Hypertension were Konstantin Kotliar (Munich, Germany) in 2011 and Stefano Masi (London, United Kingdom) in 2013.

- The next prize will be awarded during the ESH Meeting in Milan, June 12-15, 2015.

- The Servier Research Grant in Hypertension is limited to PhDs or MDs under 45 years of age on July 1 in the year of the award.

Next deadline for applications: **January 31, 2017**
Applications should be sent to: Prof Giuseppe Mancia, Clinica Medica, Ospedale San Gerardo, Via Pergolesi 33, 20052 Monza (MI), Italy
E-mail: giuseppe.mancia@unimib.it
More information is available at [www.eshonline.org](http://www.eshonline.org) and on the Servier Web site: [www.servier.com](http://www.servier.com)

- Servier, with the European Society for Microcirculation (ESM), is offering a research award: the Servier Award in Microcirculation.

- A €4000 grant is offered every 2 years for an outstanding clinical or basic research publication in the fields of microcirculation and vascular biology. The call for applications is advertised on the ESM Web site and by related societies and journals.

- The 2013 Servier Award in Microcirculation was presented to Helge Wiig (Bergen, Norway) and Agnes Schröder (Erlangen-Nürnberg, Germany) who received the prize during the 27th European Society for Microcirculation Congress in Birmingham (United Kingdom), July 21-26, 2013.

- The previous winners were Jacqueline Fields and Marc Fleury (Switzerland), Jun Yin (Toronto, Canada) and Abigail Woodfin (London, United Kingdom).

- The next prize will be awarded during the 28th European Society for Microcirculation Congress in Pisa (Italy), June 3-6, 2015.

- Applications should be submitted no later than September 30, 2016, and will be reviewed by a committee of 8 members including officers of the ESM. Scientists under 40 years of age on January 31 in the year of the award may apply.

Next deadline for applications: **September 30, 2016**
Applications should be sent to the ESM general secretary
Prof Akos Koller: akos.koller@asok.pta.hu
More information is available on the ESM website: [www.esmicrocirculation.eu](http://www.esmicrocirculation.eu)
and on the Servier website: [www.servier.com](http://www.servier.com)

For further information and deadline applications please visit our Web site:
[www.servier.com](http://www.servier.com)
Can biomarkers guide the assessment and management of heart failure patients after discharge from hospitals?

1. E. A. Bocchi, Brazil
2. D. A. Brito, Portugal
3. O. Chioncel, Romania
4. A. Fong, Malaysia
5. M. Hülsmann, Austria
6. E. A. Jankowska, Poland
7. M. Loutfi, Egypt
8. A. Lupi, Italy
9. Y. F. M. Nosir, Egypt
10. E. B. Reyes, Philippines
11. S. N. Tereschenko, Russia
12. M. B. Yilmaz, Turkey
13. B. Yoo, Republic of Korea

Despite increasing evidence on existing biomarkers and constant discovery of new biomarkers, their actual usefulness in heart failure is not yet clear. Currently, they are mainly used to improve diagnostic performance or for risk stratification and to determine prognosis. However, the value of biomarkers in daily practice is less well described and surprisingly few data are available regarding their usefulness in clinical assessment and choice of therapy for patients after hospital discharge.
Epidemiological data have shown 39.4% of total hospital admissions to be related to decompensated heart failure (HF). Despite improvement during in-hospital treatment, HF patients frequently present with severe events after hospital discharge. It has been reported that over a period of 4.7±1.6 months, 36% of discharged decompensated HF patients were readmitted. In the EVEREST trial (Efficacy of Vasopressin Antagonism in Heart Failure: outcome Study with Tolvaptan), of all rehospitalizations, 46.3% were for HF. This immediate postdischarge risk period has been termed the “vulnerable phase” of HF.

Early readmission of discharged patients with HF is challenging to predict. The focus has been primarily on quality improvement measures to assure patient education, checklist discharge, physician adherence to evidence-based HF medications, follow-up appointments within 7 to 14 days of discharge and/or telephone follow-up within 3 days of discharge, and use of clinical risk-prediction tools and/or biomarkers to identify higher-risk patients.

It is important to recognize that many patients after discharge may be “flying under the radar,” without clinical congestion, but with elevated left ventricular filling pressures or comorbidities leading to a high risk of hospital readmission. Aside from residual clinical impairment with persistent signs and symptoms of congestion, biomarkers have been examined as potential predictors for HF readmission. Measurement of circulating natriuretic peptide (NP) levels seems to add incremental prognostic information to standard clinical risk stratification algorithms for both ambulatory and hospitalized HF patients, with a steady increase in the risk of mortality and recurrent HF hospitalization in relation to increment in NP levels.

Despite the widespread use of B-type NP (BNP) assays for diagnosis of HF, there remains a lack of well-defined and accepted diagnostic and prognostic cutoff values. Additionally, elevations in NP levels can occur as a result of several cardiac and noncardiac disease states, making the negative predictive value of the test most clinically helpful.

A plethora of candidate biomarkers now exist that reflect different aspects of HF pathology, with theoretical roles in diagnosis, risk assessment, and therapeutic tailoring, but data is still required from testing within clinical trials. Serum sodium, BNP levels, net reduction in N-terminal proBNP at discharge, creatinine, albumin, hemoglobin, C-reactive protein, troponin, systolic blood pressure, and heart rate seem to be predictive of 30-day readmission for HF. In the EVEREST trial, heart rate values ≥70 beats per minute (bpm) measured at either 1 or 4 weeks after discharge were independently associated with all-cause mortality, with a 13% increase in risk of death for every 5-beat increase in heart rate (P=0.002) measured at 1 week or 12% for such increase in heart rate (P=0.001) measured at 4 weeks. A discharge heart rate greater than 80 bpm was associated with greater risk of all-cause mortality during 1 year of follow-up and an elevated risk of 30-day readmission for HF. Reducing heart rate with ivabradine is beneficial in chronic HF, decreasing hospitalization and HF mortality.

References
Most studies on biomarkers in heart failure (HF) report their prognostic value, but their use in clinical practice is not well established and should be based on clinical outcomes. Hospitalized HF patients have high post-discharge mortality and rehospitalization rates even when treated with evidence-based therapies and early postdischarge follow-up. The first 2 months after discharge are a particularly vulnerable period, with mortality and readmission rates approaching 15% and 30%, respectively, 30 to 60 days post-discharge; 1 in 4 patients are readmitted within 30 days. Recurrent HF and related cardiovascular conditions account for about half of readmissions and, overall, postdischarge readmission and mortality rates for HF remain similar whether ejection fraction (EF) is reduced or preserved. Measures to prevent early readmission or death must begin during hospitalization and extend through the early recovery period to reduce the risk of adverse events.

Some biomarkers, including low serum sodium and high aldosterone and natriuretic peptide (NP) levels, at admission and soon after discharge, help to predict early (within 90 days) readmission and death and to identify a subset of higher-risk patients that may benefit from specific targeted therapies. Congestion is the single most important contributor to readmission and a crucial target for therapy. Subclinical congestion (elevated left ventricular [LV] filling pressures in the absence of clinical manifestations) may precede clinical congestion by days to weeks or be present at discharge. Of the HF biomarkers, the B-type NPs—BNP and N-terminal proBNP—have been studied most. High levels of NPs at discharge reflect elevated LV filling pressures and correlate with readmissions in the early postdischarge period. NPs are thus useful as a marker for persistent congestion demanding further investigation and changes in diuretic dosing strategies.

Nevertheless, the role of NP levels in routine long-term HF monitoring is still under debate, though meta-analysis of published data suggests that NP-guided treatment as compared with intensive clinical management alone may indeed translate into better outcomes. In chronic HF patients (mainly with reduced EF) receiving optimized pharmacologic HF therapy, NP-guided treatment was associated with a significant and consistent benefit in HF-related hospitalization, the main morbidity outcome in HF patients across all age groups. A mortality benefit was also observed, but was confined to younger patients (<75 years of age).

Overall, published studies tell us that individual tailoring of therapy in chronic HF, guided by NP measurements, allows better adjustment of recommended doses of drugs already proven to favorably affect prognosis. However, close follow-up by trained HF practitioners able to interpret, integrate, and react to peptide levels in the overall clinical context—particularly in the older (and more vulnerable) patient—may itself promote optimization of proven therapies and prevention of adverse outcomes, independently of biomarker use to guide HF therapy in the long term.

Although NPs are the most extensively studied biomarkers in HF, several others provide important insights into different aspects of the pathophysiology of the syndrome. These may provide additional prognostic information to that afforded by NPs and may also play a role in guiding treatment and be useful for therapy selection. Galectin-3 (Gal-3), a fibrosis biomarker, is one example, potentially allowing the identification of HF patients who may benefit from specific therapies. Although not yet proven, mineralocorticoid receptor antagonists (MRAs) may confer a greater benefit in HF patients with raised Gal-3 levels than in those with lower levels. MRAs favorably affect prognosis in HF, in both the long and short term, significantly reducing the early readmission rate for HF.

The evaluation of multimarker strategies to guide therapy or to provide a comprehensive understanding of how to select therapy would certainly contribute toward better outcomes in HF patients.

References

3. Gheorghiade M, Pang PS, Ambrosy AP, et al. A comprehensive, longitudinal description of the in-hospital and post-discharge clinical, laboratory, and neurohormonal course of patients with heart failure who die or are re-hospitalized within 90 days: analysis from the EVEREST trial. Heart Fail Rev. 2012;17:485-509.

Biomarkers-postdischarge assessment and management of heart failure patients

MEDICOGRAFIA, Vol 37 , No. 2, 2015

173

2. D. A. Brito, Portugal

Dulce Alves BRITO, MD, PhD, FESC
Professor, Department of Cardiology
Hospital Universitário de Santa Maria
Lisbon Academic Medical Centre, CCUL
Av. Prof. Egas Moniz
1649-035 Lisboa
PORTUGAL
(e-mail: dulcebrito@spc.pt)
Following hospitalization for heart failure (HF), patients are at a significantly increased risk for adverse outcomes, with mortality rates as high as 10% to 15% and hospitalization rates up to 30% 3 months after discharge. Identifying high-risk patients following hospitalization is essential, given the opportunity to aggressively treat these patients and to improve their outcomes.

Biomarkers may help identify patients at increased risk for postdischarge adverse outcomes, and monitoring serial values in the outpatient setting may allow for early intervention aimed at reducing deaths and readmissions. Natriuretic peptides (NPs)—B-type NP and its N-terminal prohormone—are the most commonly used biomarkers with the potential to guide therapy. Plasma NP concentrations reflect cardiac structure and function and are prognostic in both acute and chronic HF. NP variations generally parallel responses to anti-HF therapies, and increasing concentrations are associated with poorer outcomes. Using NP levels to guide therapy is attractive, as it offers the possibility to individualize therapy according to an objective measure of function and risk. This strategy targets patients with high NP levels, at higher risk for adverse events, to receive higher doses of medications proven to increase survival.

The concept of NP-guided HF therapy has been examined in recent trials. A majority of enrolled patients had a left ventricular ejection fraction (LVEF) under 45%, and patients with significant comorbidities were excluded. Although the trial results suggest a potential benefit in the NP-guided—therapy arm, improving all-cause mortality and decreasing HF-related readmissions, NP-guided care was ineffective in preventing noncardiovascular readmissions. The target-peptide concentrations, the time point of measurement, and the aggressiveness of therapy adjustment, which varied substantially across the trials, could contribute to the presence or absence of a benefit. Current trial data have shown the benefit of NP-guided therapy to be confined to patients under 75 years old. However, with increasing age, a higher proportion of patients with HF will have a preserved LVEF (HFPEF) and multiple associated comorbidities. Although the latest published meta-analysis did not report an interaction with LVEF, it should be noted that only 10% of the patients had HFPEF at study enrollment. HFPEF has no pharmacotherapy proven to improve mortality rates and increasing doses of drugs that are ineffective is probably harmful. Although NP-guided therapy facilitates optimization of treatment and improves mortality and HF-related readmissions in selected patients, there are no convincing data to suggest that routine NP-guided therapy should be applied to all HF patients. Serial changes in NPs should be interpreted within the entire clinical context, including age, presence of comorbidities, and accounting for “intrinsic biologic variability.” Though well tolerated in the trial population, without excess risk of adverse outcomes related to therapy intensification, safety of NP-guided care should be considered in the broad HF population. NP-guided care appears to be cost effective by reducing HF hospitalization, but that should be confirmed in different health care systems.

Future research will be needed to clarify the type and magnitude of therapeutic response to the release of biomarkers. Most importantly, what should be done once patients at highest risk for postdischarge adverse events are identified? All advocated interventions—intensification of oral therapies, addition of intravenous medications, follow-up visits—are generic measures, and no supporting evidence has demonstrated any specific intervention to be more effective in lowering target NP levels. Secondly, what would be the most appropriate approach if NPs fail to decrease following intensification of therapy? Thirdly, despite decreasing NP levels, some patients may have other elements of high risk such as high troponin or high cystatin C.

In HF, a single biomarker reflects only one pathophysiological pathway. A multimarker panel investigating multiple pathological processes and probing therapeutic options would be an ideal strategy, but will need further investigation.

**References**

Even in the era of advanced therapeutics, hospital readmission rates for patients admitted with heart failure remain high. Approximately 22% of patients are readmitted within 30 days, and more than 50% are readmitted within 6 months.\(^1,2\) The cost of rehospitalization and the clinical morbidity associated with hospitalization generate demand for strategies to improve the management of patients discharged with heart failure. Heart failure clinics in the community have already made a positive impact on improving patient outcomes;\(^3\) but with rising numbers of patients being hospitalized with heart failure, quantifiable blood biomarkers are increasingly used to discriminate those at greatest risk of rehospitalization and cardiac death after discharge.

In the last decade, the principle biomarkers that have aided clinical decision making in patients with heart failure were the natriuretic peptides (NPs)—B-type NP (BNP) and N-terminal proBNP. In patients admitted with heart failure, NPs have been shown to be useful in identification of those at highest risk for rehospitalization.\(^4,5\) High NP levels, eg, a predischarge BNP level >700 ng/L has been associated with a death or readmission rate of approximately 50% 30 days postdischarge and roughly 80% at 6 months.

Conversely, a predischarge BNP level <350 ng/L was associated with a death or readmission rate of less than 5% 30 days postdischarge and <20% at 6 months. As NPs reflect the physiological status associated with myocardial strain, this information can enable clinicians to adapt the monitoring strategy accordingly, thus adopting a more aggressive strategy in those patients with the highest cardiac event risk in the outpatient clinic setting.

NPs can now be reliably measured using validated point-of-care devices. These can be placed in hospital wards or in the clinics, allowing the health care professional to obtain a timely result so that a management strategy can be more carefully constructed. In addition to the predischarge NP reading, serial monitoring of NPs provides clinicians with a “biochemical monitoring system” facilitating titration of treatment for heart failure patients. In this way, treatment can be optimized before patients experience decompensation and require subsequent hospital admission. Extending this concept further, a home-monitoring program for natriuretic testing is now under investigation, although pilot studies showing encouraging results are already available.\(^6\)

Of all blood biomarkers in clinical practice, the positive role of NP assessment in patients with heart failure is now clearly defined. The additional information it provides to both the health care provider and the patient empowers all parties to optimize the postdischarge management of heart failure patients.

References
Patients admitted for decompensation are very heterogeneous in respect to underlying cause and to severity of disease. More importantly, in-hospital treatment success is a prerequisite of postdischarge outcome. Therefore, risk assessment at discharge is necessary for decision making in the vulnerable phase afterwards. In a time of limited economic resources, there are competing interests between care of high- and low-risk patients. Relatedly, length of hospital stay (LOS), which differs up to threefold between various countries, has already become an end point marker of treatment.1

Currently, LOS correlates neither with the severity of heart failure—reflected by N-terminal pro-B-type natriuretic peptide (NT-proBNP) at entrance—nor with postdischarge outcome, implying that the time of discharge might be more influenced by cost effectiveness than evidence. Thus, there is an imminent need to change LOS policy. NT-proBNP is an excellent surrogate for treatment success, especially in acute heart failure. Bettencourt and colleagues2 proved that NT-proBNP level over time is the most favorable variable to detect treatment success. Compared with a >30% decrease in NT-proBNP during hospital stay, there is a 6-fold increase in worse outcome if NT-proBNP increases more than 30%. These results show the importance of using NT-proBNP monitoring to guide treatment and, consecutively, hospital stay. If there is no significant decrease in NT-proBNP following intervention, treatment should be scrutinized as to the expense of hospital stay. On the other hand, a rapid decrease in NT-proBNP level allows a safe and rapid discharge. Consequently, an uncritical discharge policy influences postdischarge outcome and decreases the cost effectiveness of care, something that can be optimized by a biomarker-guided approach.

Predischarge stability can directly affect postdischarge management. After discharge, there is a need for optimization of oral therapy, which has to be done during postdischarge care. A multidisciplinary approach during this period could be attractive.3 Such an approach would include, in particular, an educational program, aside from intensified collaborative care by nurses and doctors. Just after discharge, patients and their families are open to self-care education, hoping to avoid rehospitalization. Data on the effectiveness of such programs are conflicting and appear to depend on duration of the program and severity of the disease. Predischarge NT-proBNP is directly correlated with postdischarge outcome.4 Thus, preselection of patients according to NT-proBNP level might be useful in this context, to identify those patients most likely to gain the greatest benefit. Biomarker-guided therapy is shown to be effective in various settings.5 Some studies did not prove efficacy, but meta-analysis was very “noisy.” Thus, data from an ongoing large, randomized trial by Felker et al (NCT01685840) are awaited for final answers. One of those studies combined a multidisciplinary approach and guided therapy in patients following discharge.6 The investigator used NT-proBNP at discharge as a selection parameter to identify high-risk patients and used it to guide intensity of care and treatment during the following vulnerable phase. Depending on the NT-proBNP level, measured at discharge and over time, consultations by the nurse and by the heart failure specialist were initiated if the level remained elevated or, in the event of a low level at discharge, reduced. This strategy significantly reduced event rates compared with controls and with pure multidisciplinary care, but also had cost-saving effects despite increasing numbers of consultations and drug prescriptions.6 It appears that such a risk-selected treatment approach matches the right intervention to the right patient, thus avoiding under- and overtreatment.

In conclusion, NT-proBNP levels indicate the right moment for discharge following decompensation, which is crucial to further disease management. Furthermore, treatment guided by NT-proBNP levels can ensure the patient receives an appropriate intensity of care, which might save lives and money. ■

**References**

R
current hospitalization among patients with heart failure (HF) is unanimously considered the clinically crucial issue in both cardiovascular and general medicine today. Recent years have seen numerous attempts to develop optimally targeted treatment strategies aiming to relieve symptoms and improve in-hospital and long-term prognosis. Unfortunately, most have failed, providing no breakthrough in the management of acute HF.

Despite optimal treatment with life-saving drugs and devices, on discharge from hospitalization for circulatory decompensation, HF patients have an extremely high cardiovascular risk and are characterized by an enormous risk of recurrent hospitalization due to HF progression. Most importantly, the history of HF and related prognosis in these patients is very heterogeneous, and available diagnostic tools are imperfect with regard to precise individualized risk stratification.

Therefore, biomarkers have been put forward as potential additional, measurable (objective) indicators of clinical status and its dynamic changes in patients with acute HF. In this context, a comprehensive assessment (comprising clinical features and a set of biomarkers) performed after preliminary circulatory stabilization and directly before discharge is a particularly attractive concept.

For the last 20 years, biomarker research has garnered a huge amount of attention. The vast majority of related publications have concerned different aspects of the potential clinical applicability of various biomarkers in HF patients, including the natriuretic peptides (NPs) and numerous others. Along with the many publications in this field, a huge amount of scientific data on biomarkers in acute HF has been generated. Several biomarkers were shown to be related to HF severity and to predict short- and long-term outcomes; however, most of these papers provided no unequivocal and practically applicable evidence. Although the concept of the biomarker-guided diagnosis and treatment of patients with HF has been theoretically proposed, particularly for acute HF, there is as yet no hard evidence that any classical biomarker (including the NPs) can be used to guide future therapeutic decisions.

On the other hand, biomarkers allow diagnosis of some comorbidities. According to the European Society of Cardiology guidelines, active screening for comorbidities and their optimal treatment is crucial for patients with HF and could constitute an element of a comprehensive assessment before postdecompensation discharge. For example, biomarkers of iron status allow diagnosis of iron deficiency (ID) and identify those who can be effectively supplemented. Of acute HF patients, 37% have ID, which unfavorably affects their 12-month survival and could constitute a potential therapeutic target.

Notably, the definition of a biomarker is somewhat open. For example, consider the following 2 approaches. According to the traditional, strict definition, a biomarker is a molecule measured in various samples (blood, urine, etc), which provides a certain specificity and sensitivity for the diagnosis of any pathology and/or for the prediction of a particular event, success/failure in therapy, etc. However, from a broader perspective, a biomarker can be considered a measure of any quantifiable biological signal/sign.

In this context, a measure of body weight, blood pressure, or heart rate during circulatory decompensation, at discharge, and during follow-up potentially offers prognostic information, but could also be considered a therapeutic target. The prime example here could be resting heart rate. In a study of patients hospitalized for HF with a left ventricular ejection fraction ≤40% and who are not in atrial fibrillation/flutter or pacemaker dependent (participants of the EVEREST trial [Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan]), an increase in heart rate ≥70 beats per min in both 1- and 4-week postdischarge assessment was associated with increased all-cause mortality. In order to reverse this unfavorable phenomenon in such patients, it seems reasonable to consider pharmacological treatment to reduce resting heart rate during the early postdischarge phase using a β-blocker and/or ivabradine.

References
Heart failure (HF) is a chronic disease associated with a high symptom burden, and poor health status is common.1 Cardiac biomarkers, which are objective, reproducible, and accessible, are excellent adjuncts to physical examination and imaging studies in HF diagnosis and risk stratification. With a high prevalence of comorbidities associated with HF, an integrated approach utilizing multiple biomarkers has shown promise in better risk stratification, prediction of mortality, and reduction in rehospitalizations, thus lowering health care costs.

The number of biomarker studies in HF is exploding. Currently, among the available biomarkers, 5 could be used for assessment of HF prognosis, as single markers or clustered in a panel: B-type natriuretic peptide (BNP), N-terminal proBNP, (NT-proBNP), high-sensitivity cardiac troponin (hs-cTn), cystatin C, the tumor marker carbohydrate antigen 125 (CA125), and high-sensitivity C-reactive protein (hs-CRP).

BNPs provide independent prognostic information regarding estimated risk of disease progression, hospital readmission, and mortality.2 Bayes-Genis et al reported that among patients hospitalized with acute HF, those who experienced complications had a smaller percentage reduction in NT-proBNP during admission.3 Apart from the BNPs, hs-cTn assays will improve risk stratification in HF compared with conventional Tn tests. In patients with decompensated HF, serial increases in Tnl during the course of hospitalization were associated with higher mortality than stable or decreasing Tnl levels.3,4 Cystatin C, aside from its use in estimation of renal function, could also be used as a cardiac marker, as it reflects extracellular matrix pathology of ventricles.5 Recently, increased levels of serum CA125, a marker of congestion that indicates the degree of volume overload, have been documented in patients with HF.6 Finally, the biomarker hs-CRP can be used to evaluate progression of HF, due to the inflammatory etiology of the condition. Patients with acute HF and increased levels of both hs-CRP and NT-proBNP had worse clinical outcomes.7

It is possible that the combination of neurohumoral and inflammatory markers could provide a better strategy for risk stratification of patients with acute HF. Moreover, use of a single biomarker reflects only 1 ongoing pathophysiological pathway. The combination of biomarkers in a multimarker panel reflects several ongoing pathological processes, providing an increasingly clearer risk profile for HF patients.

Biomarkers not only serve as traditional predictors of prognosis, they can also help to identify high-risk patients who need closer monitoring and more aggressive therapy. An integrated approach utilizing multiple biomarkers has shown promise in predicting mortality, in risk stratification, and in reducing rehospitalizations, with subsequent improvement in the effectiveness of HF therapy and patient outcomes.

References
Heart failure (HF) is a clinically challenging syndrome, with different etiologies according to patient age and coexisting comorbidities. Such heterogeneity is associated with different HF stages, affecting patient prognosis and therapeutic response. However, diagnosis and prognostic stratification based purely on clinical features has shown limited accuracy, often accounting for suboptimal therapy and high rates of hospital readmission and mortality. Thus, the efforts of clinical researchers have been polarized toward the development of more reliable HF laboratory markers.

This research has profoundly benefited from increased knowledge in the pathophysiology of cardiac failure: myocyte degradation caused by oxidative stress, injury and apoptosis, inflammation, neurohumoral upregulation, and excessive proliferation of the extracellular matrix are phenomena that can all be tracked with a multitude of biomarkers. However, despite the recent hyperbolic increase in published studies on HF biomarkers, their actual clinical usefulness is still unclear, accounting for the need of convenient frameworks in which these markers might be used in a cost-effective manner.

Among the numerous biomarkers proposed for guiding therapeutic optimization and postdischarge management of HF patients, only a few have been extensively studied and can currently be assessed with reasonable practicality. B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are by-products of the myocardial endocrine secretion of mediators in response to left ventricular dysfunction and mechanical stress. Increased levels of NPs at discharge have been associated with higher readmission rates for HF, thus measurement of such markers after clinical resolution of HF has been proposed for guidance of therapeutic optimization before and after discharge.

Guided therapy was addressed by a few nonrandomized studies that produced contrasting results. Moreover, these studies did not present enough statistical power to detect any significant difference in hard end points. To overcome these limitations, these studies were pooled into 2 meta-analyses, which suggested a mortality reduction in patients treated with NP-guided therapy (NP-GT), but no apparent reduction in rehospitalization rates.

These results cannot be directly translated into daily clinical practice for several reasons. First of all, NP-GT studies preferentially enrolled patients with systolic dysfunction of ischemic origin, excluding HF cases with preserved ejection fraction and nonischemic cardiomyopathies. Moreover, different NP goals influenced the final results of NP-GT studies, with better outcomes in those aiming to lower NP levels. In many patients, NP levels did not respond to NP-GT, generally in subjects aged over 75 years. Actually, no randomized trial with sufficient statistical power using NP guidance in acute HF treatment has been published thus far and we currently do not have firm evidence from prospectively-defined published trials that the addition of NP-GT is beneficial. However, taking all the evidence into account, the American Heart Association (AHA)/American College of Cardiology (ACC) 2013 guidelines placed NP-GT in class 2a with a level of evidence B. From a practical point of view, it seems reasonable to routinely collect baseline and predischARGE NP samples in hospitalized HF patients, with those showing a <30% reduction in NP level from baseline considered to be at higher risk of hospital readmission and thus treated with more aggressive management. Other available biomarkers, such as high-sensitivity C-reactive protein (hs-CRP), the tumor marker carbohydrate antigen 125 (CA125), and high-sensitivity cardiac troponins, are increased in HF patients, but their role in optimizing HF therapy and guiding hospital discharge seems to be limited.

In conclusion, HF biomarkers could potentially guide therapy in HF patients after hospital discharge on an outpatient basis, but the few studies conducted in this area have conflicting results. A large, prospective, controlled study, statistically powered to look at hard end points such as mortality is warranted before the scientific community can reach any consensus on this approach.

References
9. Y. F. M. Nosir, Egypt

Heart failure (HF) prevalence is increasing and remains the leading cause of death worldwide, causing a significant burden on health care systems across the globe. Currently, there is no reliable objective guide to optimal pharmacotherapy in HF. Despite clear treatment guidelines, target doses for medications are often not achieved. Clinical assessment is insensitive and frequently does not identify hemodynamic decomposition.

Biomarkers, with their objectivity and widespread availability, have a promising role in improving HF management. The natriuretic peptides (NPs) are the most widely used biomarkers of myocardial strain. These include B-type NP (BNP) and the N-terminal fragment of its prohormone (NT-proBNP), as well as atrial NP (ANP), and the mid-regional fragment of its prohormone (MR-proANP), and adrenomedullin.1 Cardiac troponin (cTn) levels and their assays (cTnl vs cTnT) have also been evaluated in ambulatory patients with stable coronary artery disease (CAD).2 In many studies, there is a >10-fold increase in the proportion of subjects with detectable cTn levels when utilizing a high sensitivity (hs) assay.2 In randomized controlled trials of statins and angiotensin-converting enzyme inhibitors versus placebo, NPs consistently and independently identified subjects with increased risk. The same was found true of cTnl and cTnT.2

Tailoring HF treatment to achieve a target level of BNP was first tested in the late 1990s.3 Since then, a series of studies using a variety of study designs have addressed this strategy.4 To date, there is little evidence to support using elevated levels of either NPs or cTns to guide therapy. It may be that no 1 biomarker fits all in this heterogeneous population with known CAD.5 However, plasma levels of both peptides reflect cardiac function and filling pressures and are powerful predictors of mortality.4

Serial peptide measurements provide incremental prognostic value in both the in- and outpatient setting, with a fall in peptide levels being associated with better outcomes.4-6 In the largest of these studies, TIMECHF (Trial of Intensified vs standard Medical therapy in Elderly patients with Congestive HF), a higher NT-proBNP level was used as a target for subjects over 75 years of age (800 pg/mL) compared with those ages 60 to 74 years (400 pg/mL). Some significant clinical benefit was shown with biomarker-guided management, at least in younger patients.4

The PRIMA study (Can PRo-brain-natriuretic peptide guided therapy of chronic heart failure Improve heart Failure morbidity and mortality?)6 looked at an individualized NT-proBNP target in 345 patients who had been hospitalized with decompensated HF. The target NT-proBNP level was ≤1700 pg/mL. Additionally, subjects had to achieve a >10% decrease and at least a 850 pg/mL reduction in NT-proBNP during hospitalization. For the 174 subjects randomized to the NT-proBNP–guided group, an individualized target NT-proBNP level was identified based on the lowest NT-proBNP level obtained at discharge or within 2 weeks after discharge. Uptitration of treatment was triggered if the NT-proBNP level at scheduled 3-monthly visits was more than 10% and at least 850 pg/mL above their individual baseline level. For the 171 subjects in the comparator clinically guided group, treatment was uptitrated on the basis of standard clinical assessment. After a median follow-up of 702 days, there was greater uptitration of treatment in the NT-proBNP–guided group at 1-year follow-up. The investigators observed fewer deaths in the NT-proBNP–guided group, particularly in patients under 75 years of age and in those with reduced ejection fraction below 45%.5,6

Currently available data showed usefulness of biomarkers in HF management through achieving target dosage of medication with a trend in reducing mortality. Further data are needed from more robust, adequately powered trials before guidelines can confidently endorse a biomarker-guided strategy in HF management.

References
Heart failure (HF) is a syndrome with a wide spectrum of clinical manifestations: from asymptomatic to full-blown congestive failure; from normal ejection fraction (EF), ie, HF with preserved EF (HFPEF), to very low EF, ie, heart failure with reduced EF (HFREF); from acute onset to gradual onset and chronic conditions. Etiologies and comorbidities are also diverse, and there can be puzzling differences in response to therapies.

At the end of the spectrum is severe symptomatic systolic HF, which is quite easy to diagnose and prognosticate, with clinical assessment as a key basis for choosing diagnostics and treatment. However, gray zones are found in mild dis-

Left ventricular EF (LVEF), is a useful parameter in assessing LV pump performance, especially now that echocardiography is readily accessible. When LVEF is reduced (<45%), it is a powerful and useful prognostic and monitoring parameter. However, LVEF plateaus over time and has limited utility in HFPEF.

In the last 2 decades, an explosion in research paved the way to the use of biomarkers as clinical guidance in the management for HF—an example of knowledge translation from clinical evidence to patient care—to close the gap emanating from the limitations of using pure clinical assessment in making therapeutic decisions. One such gap is the low utilization of guideline-directed therapy to optimize patient care, which may be due to low awareness or competence in applying such therapy.

Biomarkers for HF include markers for myocyte stretch (eg, B-type natriuretic peptide [BNP] and atrial NP), myocyte remodeling (eg, ST2 protein and galactin), inflammation (eg, interleukin 6 and Fas), neurohormonal activation (eg, endothelin), and comorbidities (eg, procalcitonin for infection, and neutrophil gelatinase-associated lipocalin for kidney failure). All of these are elevated in clinical HF and can define the presence of HF or other diseases that may mimic HF. The best studied markers are BNP and N-terminal proBNP.

There are at least 11 randomized controlled studies that compared NP-guided therapy vs therapy guided by pure clinical assessment. The studies were all small (ranging from 69 to 499 included patients) and results of individual trials, though positive, were not convincing. A meta-analysis showed that the hazard ratio for total mortality was 0.82 (95% confidence interval [CI], 0.62–1.00), with the CI touching the line of unity. However, the hazard ratio for rehospitalization was reduced significantly by 26% (0.74; 95% CI, 0.60–0.90). This reduction could be attributed to a 7% absolute increase in the proportion of patients who received targeted doses of angiotensin-conv-

Clearly, biomarker-guided therapy in HF is possible, but the findings from randomized trials are not convincing enough to recommend its routine use. Its weakness lies in the fact that it does not tell you which medications to adjust and so we go back to clinical assessment. Furthermore, NP testing is costly and target levels and frequency of testing have not been standardized. The latest guidelines on HF recommend the use of biomarkers for risk stratification. The recommendations on the use of biomarkers as a guide in maximizing medical therapy are weak, but do not prohibit physicians from using them as guides. A large randomized trial is needed to address this gap.

References
1. De Keulenaer GW, Brutsaert DL. The heart failure spectrum: time for a pheno-
3. Troughton RW, Frampton CM, Brunner-La Rocca HP, et al. Effect of B-type na-
4. Yancy CW, Jessup M, Bozkurt B, et al; American College of Cardiology Founda-
tion; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/ AHA guideline for the management of heart failure: a report of the American Col-
lege of Cardiology Foundation/American Heart Association Task Force on Prac-
5. McMurray JJ, Adamopoulos S, Anker SD, et al; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology. Eur Heart J. 2012;33:1787-1847.
To date, the B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are among the most studied biomarkers. An increased level of NP is directly associated with hemodynamic stress. In HF, a high NP level at hospital discharge is an independent marker of poor prognosis (death and HF decompensation).

The significance of NPs for risk stratification in HF patients has been shown in both inpatients and outpatients. These biomarkers represent a “gold standard” in prognostic evaluation. According to Val-HeFT (the Valsartan in Heart Failure Trial), the cutoff values for BNP and NT-proBNP in stable HF patients are 125 pg/mL and 1000 pg/mL, respectively.1 More prognostic information can be obtained by serial measurements. In general, a reduction in NP levels below a specified value predicts fewer hospital admissions or reduced mortality risk. According to a study by Doust et al, each 100 pg/mL increase in BNP level is associated with a 35% increase in mortality risk.2

A study by Berger et al included 278 patients with uncompensated HF, who were randomized at discharge using the NT-proBNP cutoff value of >2200 pg/mL into 3 groups: (i) personalized treatment (with NT-proBNP level reduction below 2200 pg/mL), (ii) intensive patient management using the multidisciplinary care (MC) approach, and (iii) conventional treatment. Once the target NT-proBNP level was achieved, patients were treated according to standards of the MC group. However, in case of an increase in NT-proBNP level, patients received NP-guided treatment. Main end points included HF hospitalization, time to death or HF rehospitalization, time to first HF rehospitalisation, and death. During follow-up, the NP-guided group received more aggressive therapy than the other 2 groups: a higher proportion of patients were on triple therapy, and doses were ≥50% of target doses. As a result, this group showed the greatest reduction in NT-proBNP level by the end of follow-up. In general, these patients remained clinically more stable throughout the study and had significantly fewer days of hospitalization due to decompensated HF (P=0.0001). Moreover, with the NP-guided approach, risk of the combined end point of death/HF rehospitalization at 18 months was reduced by 37% (vs 50% in the MC group and 65% in the conventional treatment group; P<0.05). The mortality rate in the NP-guided group was the same as in the MC group (22%) and was significantly lower than in the conventional treatment group (39%; P=0.02).

This study is of extreme value. It is well known that HF patients with persistently high NP concentrations at discharge after hospitalization due to decompensated HF have a higher risk of death and HF rehospitalization. Thus, these patients require a particular approach to treatment and control that presupposes, among other things, the reduction in NP level as a result of successful therapy.

Limiting factors include the relatively low stability of the BNP molecule, biological variability, a large “gray zone,” as well as the influence of age, sex, and body weight. Comorbidities can cause mistaken risk stratification of HF patients. In this regard, a multimarker strategy (with copeptin, galectin-3, MR-proadrenomedullin, soluble ST2 receptor, high-sensitivity [hs]-troponin, etc) is attractive, due to potential for better risk stratification of HF patients.

Will these multimarker panels have a real advantage? Will the predictive value from a combination of markers exceed that obtained from each individually and to what extent? How many markers are required, and what combination is optimal for prognostic assessment in HF patients? Nowadays, there are still many more questions than answers.

References
Can biomarkers guide the assessment and management of heart failure patients after discharge from hospitals? In the presence of an ideal biomarker, the answer would be “Yes, they can.” What is a biomarker? A biomarker is defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” Hence, anything could be a biomarker. However, in the clinical sense, measurement of a biomarker usually refers to a simple blood or urine test in most cases. Biomarkers could be used in diagnosis, prognostication, monitoring of a therapeutic response, stratification and also for some other reasons.

Heart failure (HF) is a complex, fatal disease, characterized by 2 overlapping subtypes, ie, acute and chronic HF. Acute HF represents a major challenge both to the physician and to the hospital and has a high risk of mortality and morbidity in the short term. Patients hospitalized for an attack of acute HF enter a vulnerable period after hospital discharge, during which many patients need close follow-up management. After discharge, biomarkers can be used to guide physicians. For example, choice of therapy is already guided by “safety” biomarkers, such as creatinine or potassium, as in the case of mineralocorticoid-receptor antagonist therapy.

With regard to biomarkers in HF, considerable progress has already been made. Natriuretic peptides (NPs), as quantitative biomarkers of ventricular and/or atrial loading, can serve as “near-perfect” biomarkers in the diagnosis of HF. Nevertheless, their performance in daily practice is limited despite recent efforts and well controlled studies (eg, GUIDE-IT [GUIDing Evidence based therapy using biomarker Intensified Treatment in heart failure]). First of all, quantitation of NPs is limited by test accuracy. Secondly, though a decrease/increase in NPs is linked to improvement/progression of the disease, there is considerable room for biological variation, particularly in patients with mild disease or in patients with recent acute HF. Thirdly, an ideal biomarker should either be disease specific or organ specific. However, there is a sizeable list of reasons that lead to elevation of NPs in the absence of HF. Furthermore, right ventricular function, independent from left ventricular function, adds complexity to the interpretation of elevated NPs. Last, but not least, in order for information from a biomarker to be meaningful, it should not overlap significantly with otherwise obtained basic clinical information. In the case of NPs, they may provide additional information which is useful for diagnostic purposes; however, their use in guiding therapy during follow-up has not been well established.

In conclusion, there is an unmet need for a biomarker that can help physicians tailor therapy of HF patients after discharge. Despite progress in this area, there are obstacles to overcome before integrating biomarkers into clinical decision making in the HF setting.

References
Recently, natriuretic peptide (NP) measurements after discharge from hospital have been used to provide incremental information over clinical presentation or as an end point to assess the efficacy of heart failure therapy, and as a prognostic marker in heart failure.1 However, although commercial assays are currently approved for diagnosis of heart failure, use of NPs in monitoring the success of congestive heart failure (CHF) therapy or as a therapeutic target in heart failure has not as yet been submitted for regulatory approval.2

The first question is whether B-type NP (BNP) or N-terminal proBNP (NT-proBNP) can be a treatment target in HF management. BNP levels correlate positively with cardiac filling pressures and volumes and are inversely related to left ventricular ejection fraction. After treatment, recovery of neurohormonal balance means stabilization of HF status. BNP in follow-up of heart failure patients was considered as a “biochemical Swan-Ganz catheter,” such as glycated hemoglobin (HbA1c) in patients with diabetes mellitus or alpha-fetoprotein (AFP) in patients with hepatocellular carcinoma. Because BNP levels correlate with atrial and ventricular filling pressures, it is reasonable to ask whether changes in BNP mirror the effectiveness of therapies designed to reduce filling pressures. Therefore, it is possible to accept BNP or NT-proBNP as a good target for treatment of heart failure, one that is objective, reliable, practical, and inexpensive.1

The second question is how results of serial measurements of BNP or NT-proBNP should be interpreted in the outpatient clinic. In the Val-HeFT study (Valsartan in Heart Failure Trial), high baseline values of BNP were related to high mortality, and after 4 months, patients with a large reduction (% change) in BNP had a relatively lower risk than other groups.3 In the outpatient setting, symptoms that suggest early decompensation and a rising BNP level should trigger either a clinic visit or diuretic adjustment. BNP level measured in the outpatient clinic may be a reliable monitoring marker, taking into consideration the following advantages: results are obtained quickly, it is not affected by eating or exercise, it facilitates diuretic adjustment early after discharge, and it reflects exacerbation or success of treatment.1

The final question is about BNP- or NT-proBNP–guided therapy in HF. The dynamic nature of BNP and NT-proBNP relative to therapeutic intervention in HF has led to the concept of using the biomarkers as a “guide” for intensification of HF care. The aim would be not only to achieve guideline-directed medical therapy goals, but to target NP itself, suppressing it below prognostic thresholds.4 During the last decade or more, the concept of biomarker-guided management of HF based on NP targets has been an intriguing and controversial topic.2 Nevertheless, in certain studies of this BNP- or NT-proBNP–guided approach, patients treated with biomarker-guided care had superior outcomes when compared with standard heart failure management alone. This was the case particularly in younger study populations, in patients with left ventricular systolic dysfunction, and when substantial reductions in NPs were achieved in association with biomarker-guided care.1

BNP and NT-proBNP can provide significant prognostic information and it is possible that adjustment of anti–heart failure therapy according to serial measurements of BNP (in addition to standard clinical assessment) may lead to improved outcomes.4 However, randomized controlled trials have yielded inconsistent results. A better understanding of unresolved issues, including test variation, cutoff values, acceptable times for check-up, and cost effectiveness is needed before we can effectively use this valuable test in the clinical setting.1

References
Once a relatively short-term, quickly fatal condition, systolic heart failure (HF) today is a chronic disease characterized by recurrent nonfatal events (hospital admissions). With the burden of hospitalizations for HF continuing to grow, prevention of rehospitalization has become the most urgent need in cardiology. Hospital discharge is an opportunity to identify modifiable prognostic factors and to optimize patient therapy. The clinical profile of HF patients is complex, mainly due to aging and the frequent presence of noncardiovascular and cardiovascular comorbidities. These conditions not only complicate management of HF patients, but also increase risk of in-hospital and postdischarge mortality and morbidity. The important role of Procoralan (ivabradine) in the management of patients with chronic HF is well established and supported by its benefits in prevention of morbidity and mortality. Efficacy and tolerability of ivabradine in patients with HF, including those with different clinical profiles (elderly; severe disease; low blood pressure; comorbidities, including renal dysfunction, diabetes, chronic obstructive pulmonary disease) make ivabradine particularly pertinent for achievement of all targets in the treatment of HF, including improvement of symptoms and well-being, as well as outcomes. This offers the promise of a better prognosis and improved quality of life for millions of patients with chronic HF.

Medicographia. 2015;37:185-192 (see French abstract on page 192)
Procoralan: new opportunities for vulnerable HF patients – Elyubaeva

or early postdischarge provides important prognostic information. The recent analysis of a cohort of 9097 patients with HF discharged from hospital demonstrated that discharge HR was significantly associated with 30-day HF readmission—with adjusted hazard ratios of 1.26 (95% confidence interval, 1.04-1.54; \( P = 0.021 \)) in patients with the highest HR group (HR > 90 beats per minute [bpm]) compared with the reference group with a HR of 61-70 bpm.\(^3\) There was a trend in patients with HR below 60 bpm toward the lowest risk with an adjusted hazard ratio of 0.87. The trend was consistent for 30-day cardiovascular (CV) readmission, mortality, and long-term outcomes. For example, the group with the highest HR—above 80 bpm—was associated with higher risk of 1-year HF mortality (1.26; \( P = 0.023 \)) compared with the reference group with a HR lower than 60 bpm. The recent analysis from the EVEREST trial (Efficacy of Vasopressin antagonism in hEart failuRE: outcome Study with Tolvaptan)\(^4\) demonstrated that the survival curves of the patients, subdivided according to the HR measured 1 or 4 weeks after discharge, started to diverge relatively early, and continued to diverge during follow-up. These results are consistent with a long-lasting persistent effect of elevated HR on prognosis (Figure 1).\(^5\) This causal role is also consistent with the improvement in outcomes observed with pure HR reduction with ivabradine in patients with chronic HF on optimal medical treatment.

### Selected Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>bpm</td>
<td>beats per minute</td>
</tr>
<tr>
<td>CARVIVA</td>
<td>Effect of CARVedilol, IVAbradine or their combination on exercise capacity in patients with Heart Failure</td>
</tr>
<tr>
<td>CHF</td>
<td>chronic heart failure</td>
</tr>
<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CV</td>
<td>cardiovascular</td>
</tr>
<tr>
<td>DM</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>EVEREST</td>
<td>Efficacy of Vasopressin antagonism in hEart failuRE: outcome Study with Tolvaptan</td>
</tr>
<tr>
<td>HF</td>
<td>heart failure</td>
</tr>
<tr>
<td>HR</td>
<td>heart rate</td>
</tr>
<tr>
<td>INTENSIFY</td>
<td>Practical daily effectiveNess and TolEraNce of Procoralan in chronic Systolic heart Failure in GermanY</td>
</tr>
<tr>
<td>KCCQ</td>
<td>Kansas City Cardiomyopathy Questionnaire</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricular</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>RAAS</td>
<td>renin-angiotensin aldosterone system</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>RRR</td>
<td>relative risk reduction</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>SHIFT</td>
<td>Systolic Heart failure treatment with the ( I_f ) inhibitor ivabradine Trial</td>
</tr>
</tbody>
</table>

### Figure 1. Mechanisms potentially involved in the untoward effects of elevated heart rate in heart failure.

**Abbreviation:** \( O_2 \), oxygen.

*After reference 5: Metra. JACC Heart Fail. 2013;1(6):497-499. © 2013, American College of Cardiology Foundation. Published by Elsevier Inc. All rights reserved.*

Pure HR reduction with procoralan (ivabradine): anti-ischemic effect and dual cardiac and vascular protection in coronary artery disease and HF

Procoralan (ivabradine) is a specific HR-lowering agent, and is the first agent of this type to be approved for therapeutic use.\(^6\) As opposed to other HR-lowering agents, ivabradine expresses unique action on pacemaker activity in the sinoatrial node of the heart, which results in important differences between ivabradine and nonselective HR-reducing agents such as \( \beta \)-blockers. Ivabradine inhibits \( I_f \), an ionic current that modulates pacemaker activity, lowering HR without directly affecting cardiac conduction or contractility.\(^7\) Myocardial perfusion, particularly in the subendocardium, takes place almost entirely during diastole. Physiological changes in HR affect mainly the duration of diastole leading to prolongation in diastolic time at lower HR, both in absolute terms and as a fraction of the cardiac cycle, facilitating myocardial perfusion.\(^8\) Ivabradine, in common with physiological HR reduction, lowers HR essentially by prolonging diastole.\(^9\) By reducing HR, ivabradine decreases myocardial oxygen consumption and increases myocardial perfusion, both explaining the preserved
cardiac energy metabolism, which is profoundly depleted during HF. Sustained HR reduction with ivabradine improves cardiac function by significantly decreasing left ventricular (LV) systolic diameter and increasing fractional shortening.10 Ivabradine preserves cardiac output due to increased stroke volume, reduced LV collagen density, and increased LV capillary density. Similar cardiac benefits have also been observed in rats when ivabradine was given immediately after myocardial infarction, highlighting both the preventive and curative benefits of ivabradine in HF.11

These experimental data show that long-term HR reduction with ivabradine optimizes energy consumption, reverses remodeling, and prevents disease progression in HF.12 Beneficial effects of ivabradine on LV volumes have been further documented by assessing its effects on the global cardiac remodeling process involved in HF. This adaptation following myocardial injury is defined as a series of biochemical and cellular modifications, such as fibrosis and local renin-angiotensin aldosterone system (RAAS) stimulation, and electrophysiological modifications, such as alteration of sarcoplasmic reticulum calcium cycling. Nonclinical data have shown that ivabradine has a marked beneficial effect on these remodeling parameters. At the cellular level, ivabradine reduces fibrosis and local RAAS stimulation (decrease in cardiac angiotensin II type 1 receptor).13 Ivabradine reduces triggered ventricular premature complexes in chronic HF (CHF) rats in addition to a decrease in ventricular fibrosis and sympathetic drive.14

These preclinical findings show that, in several models of HF, a pathological condition in which a series of phenotypic cardiac maladaptations is progressively induced, the long-term HR-reducing properties of ivabradine prevent progression of cardiac dysfunction and optimize energy consumption. In the short term, this is associated with increased diastolic time, improved myocardial perfusion, and reduced oxygen consumption. In the long term, ivabradine induces a global reversal of remodeling and prevents endothelial dysfunction. All these mechanisms contribute to the prognostic benefits of ivabradine in patients with HF.

Clinical benefits of pure HR reduction by ivabradine in patients with LV dysfunction and HF

The results of clinical trials are consistent with the importance of HR in the pathophysiology of HF, supporting the place of ivabradine as an important part of management of patients with LV systolic dysfunction (LVSD) and HF.

◆ Improvement of symptoms and exercise capacity, and reduction in signs of decompensation in patients with HF

SHIFT (the Systolic Heart failure treatment with i, inhibitor ivabradine Trial) found that ivabradine significantly improved the New York Heart Association (NYHA) class (29.0% vs 24.2% in the placebo group; P<0.0156) and patient-reported global assessment (65.9% vs 61.3% in placebo; P<0.0345) in the overall SHIFT population.15

In the randomized, open, blinded end point CARVIVA study (Effect of CARVedilol, IVAbradine or their combination on exercise capacity in patients with Heart Failure), after 3 months of therapy with ivabradine, the NYHA class was significantly more improved in patients receiving ivabradine and combination therapy compared with those allocated to carvedilol.16 Ivabradine alone or in combination was also more effective in improvement of exercise capacity compared with carvedilol alone.

The results of the recent INTENSIFY study (Practical daily effectiveNess and TolEraNce of Procoralan in chronic Systolic heart Failure in GermanY) confirmed the clinical efficacy of ivabradine in daily practice over a 4-month period in 1956 patients with CHF.17 After 4 months, ivabradine reduced HR by 18.1±12.3 bpm to 67.1±8.9 bpm, accompanied by symptomatic improvement with a shift in NYHA classification of patients toward lower gradings (Figure 2)17 and a reduction in signs of decompensation from 23% to 5% of patients.

Figure 2. Proportion of patients in different NYHA classes over 4 months of therapy with ivabradine in patients with chronic heart failure participating in the INTENSIFY trial.

Abbreviations: INTENSIFY, Practical daily effectiveNess and TolEraNce of Procoralan in chronic Systolic heart Failure in GermanY; n, number of patients; NYHA, New York Heart Association.

Improvement of health-related quality of life in patients with HF

A substudy of the SHIFT trial in 1944 patients demonstrated that in parallel to a reduction in outcomes in the SHIFT trial, ivabradine improved health-related quality of life (HQOL) in patients with HF, assessed by the specific Kansas City Cardiomyopathy Questionnaire (KCCQ). Treatment with ivabradine significantly improved both scores measured with the KCCQ: the overall summary score (OSS) and the clinical summary score (CSS). The OSS, which includes the physical limitation, total symptom, QOL, and social limitation scores, was improved by ivabradine by 6.7 points vs 4.3 in the placebo group (P <0.001) by 12 months. The CSS, which includes the physical limitation and the total symptom domain scores, was improved by 5.0 points with ivabradine vs 3.3 in the placebo group (P=0.018) after 12 months. Qualitatively, similar benefits were found with ivabradine vs placebo at 4 months and were maintained throughout study follow-up.

The improvement of QOL was demonstrated in the randomized, open, blinded end point CARVIVA study. After 3 months of therapy, ivabradine improved QOL compared with no change with carvedilol alone.

In the recent INTENSIFY study, scores from the European quality of life-5 dimensions (EQ-5D) index and the EQ-5D visual analog scale (EQ-5D-VAS) were improved from 0.64±0.28 to 0.79±0.21 and from 0.55±0.18 to 0.70±0.16, respectively, over 4 months of therapy with ivabradine.

Reversing ventricular remodeling in patients with HF

Reversal of LV remodeling has important clinical implications as cardiac remodeling is a central feature of the progression of HF and is an established prognostic factor in patients with this condition. An echo substudy in 611 patients from SHIFT demonstrated that 8 months of therapy with ivabradine resulted in a 7 mL/m² reduction in LV end-systolic volume index (LVESVI), as compared with 0.9 mL/m² in the placebo group. The LV end-diastolic volume index (LVEDVI) was reduced by 7.9 mL/m² as compared with 1.8 mL/m² in the placebo group; LVEF was improved by 2.4%, whereas there was no change in the placebo group at all. Moreover, these results occurred despite treatment with β-blockers and RAAS inhibitors, each used in more than 90% of patients.

Further analysis from SHIFT demonstrated that HR reduction with ivabradine can directly affect the vascular system and that the reported reduction in afterload was mainly triggered by a decrease in vascular pulsatile load, whereas systemic resistance remained constant. Better arterial compliance appears to result in improved ventricular arterial coupling with a significant increase in LVEF and stroke volume, without changes in LV contractility and cardiac output (Figure 3). The beneficial impact of ivabradine on LV remodeling and function may contribute to the reduction in cardiac morbidity and mortality found in patients with HF.

Prevention of hospital admissions and mortality in patients with HF

The effect of ivabradine to improve prognosis in HF has been successfully tested in the SHIFT trial—the randomized, placebo-controlled clinical trial in 6558 patients with moderate to severe chronic HF and LV systolic dysfunction (LVEF<35%; HR≥70 bpm; with median follow-up of 22.9 months). The SHIFT trial clearly demonstrates that ivabradine offers major prognostic benefits for patients with HF on top of the best possible recommended therapy. The primary composite end point (CV death or hospital admission for worsening HF) was significantly reduced by 18% (P<0.0001). Ivabradine significantly reduced HF death (relative risk reduction [RRR], 26%; P<0.014) and hospitalization for HF (RRR, 26%; P<0.0001). Results were consistent across all subgroups, including patients with HF of ischemic and nonischemic origin (Figure 4).

On the strength of the absolute RRR of the primary end point,
26 patients would need to be treated for 1 year to prevent 1 CV death or HF-related hospital admission. CV death and all-cause death diminished by 9% and 10%, respectively, and achieved statistical significance in patients with a HR of at least 75 bpm, with 17% reduction in all-cause mortality (P=0.0109) and 17% reduction in CV mortality (P=0.0166). Prevention of HF readmission is identified today as the most urgent unmet need in cardiology. Such admissions are not only distressing for patients and their families, but are also implicated in disease progression and drive the huge economic burden of HF. The analysis from SHIFT showed that ivabradine substantially reduces the total number of HF hospitalizations by 25% (P=0.0002). Over 2 years of follow-up, ivabradine substantially reduced the risk of recurrent HF hospitalization: with a 34% (P<0.001) reduction in risk of second hospitalization and a 29% (P<0.012) reduction in risk of third hospitalization (Figure 5). Similar results for HF hospitalization were seen in the higher-risk subgroup of patients with a HR of at least 75 bpm (27% reduction; P=0.0006). Ivabradine also reduced hospitalizations for any cause (by 15%; P=0.001) and CV hospitalizations (by 16%; P=0.002).

◆ Improvement of prognosis in patients with HF with different clinical profiles

Patients with HF are characterized by the presence of multiple comorbidities or conditions, including old age and low systolic blood pressure (SBP), which not only complicates treatment strategies, but also increases the risk of undesirable side effects and worsens prognosis. Therefore, it is imperative to analyze efficacy and tolerability of medications in patients with HF with different clinical profiles.

◆ Patients with severe HF

Severe HF, ie, NYHA class IV, is associated with relatively poorer survival than patients with NYHA classes II and III. Moreover, patients with severe HF are the most difficult to treat. The analysis from the SHIFT trial explores the efficacy and safety of ivabradine in 712 patients with severe HF (NYHA class IV and/or LVEF<20%). The results indicated that the effect of ivabradine to reduce outcomes, including the primary outcome (CV mortality or hospitalization for HF), HF death, and hospitalization for worsening HF, is consistent in patients with severe and less-severe HF, with no significant statistical interaction between the results in the 2 groups. Treatment with ivabradine was also associated with improvement in NYHA functional status in patients with severe disease. Importantly, therapy with ivabradine was safe in these severe patients with no unexpected adverse events and no impact on blood pressure (BP).

The recently published study in patients with severe systolic HF who were hospitalized for worsening HF explored the use of ivabradine in the hospital setting. Ivabradine treatment was started within 6 days of admission on average. The mean

![Figure 4. Reduction in cardiovascular death or hospitalization for worsening heart failure (primary composite end point) in the pre-specified patients with systolic chronic heart failure of ischemic or nonischemic etiology in the SHIFT trial. Abbreviations: CI, confidence interval; HF, heart failure; SHIFT, Systolic Heart failure treatment with the If inhibitor Ivabradine Trial. Based on data from reference 15: Swedberg et al. Lancet. 2010;376(9744): 875-885.]](image)

![Figure 5. Estimate of the effect of ivabradine on recurrence of hospitalizations for worsening heart failure. Abbreviation: n, number of patients. After reference 24: Borer et al. Eur Heart J. 2012;33(22):2813-2820. Published on behalf of the European Society of Cardiology; All rights reserved. © 2012, The Author.)](image)
of ivabradine was comparable in the 2 groups. The HR decreased by 10.7±7.2 bpm 24 hours after ivabradine administration. The maximum HR decrease was 16.3±8.2 bpm, at discharge. A HR under 70 bpm was achieved in 50% and 80% of patients 24 hours after administration and at discharge, respectively. Thus, the decrease in HR was rapid, but sustained. There was no significant variation in BP, which explains the hemodynamic stability. Moreover, HR had a significant association with N-terminal pro-B-type natriuretic peptide (NT-proBNP) and NYHA class improvement.

**Patients with renal dysfunction**
Renal dysfunction, even transient, is common in HF patients and is a known predictor of CV outcomes and mortality in patients with cardiac disease. Worsening renal function has been associated with adverse outcomes in patients with HF, underuse of proven agents, and even discontinuation of beneficial medication.27 The analysis from SHIFT demonstrated that renal dysfunction defined as an estimated glomerular filtration rate (eGFR) under 60 mL/min was present in 24% of patients (n=1579).28 Ivabradine use was associated with a reduction in the primary composite end point of CV mortality or hospitalization for HF both in patients with (by 18% of RRR; P=0.023) or without renal dysfunction (by 19% of RRR; P<0.001) at baseline (P for interaction=0.89), and tolerability of ivabradine was comparable in the 2 groups.29 There were no differences in changes in renal function over time between ivabradine- and placebo-treated patients.

**Patients with chronic pulmonary obstructive disease**
Up to one-third of HF patients are affected with chronic obstructive pulmonary disease (COPD) and vice versa.29 Thus, it is important to know of the potential interference of COPD with any therapy in HF. Analysis from the SHIFT trial showed that COPD was present in 11% of HF patients (n=730).28 The primary end point (CV mortality or HF hospitalization) and its component, hospitalization for worsening HF, were more frequent in COPD patients (hazard ratios 1.22, P=0.006; and 1.34, P<0.001; respectively), but relative risk (RR) was reduced similarly by ivabradine in both COPD (14% and 17%) and non-COPD (18% and 27%) patients (P interaction=0.82 and 0.53, respectively). Ivabradine was similarly safe in chronic HF patients with or without COPD.

**Patients with low BP**
Of HF patients, 15% to 25% have low SBP (ie, <120 mm Hg), and are at greater risk of in-hospital and postdischarge mortality and morbidity.30 Moreover, the presence of low SBP complicates the management of HF, as many guideline-recommended HF medications also lower SBP, such as β-blockers and angiotensin-converting enzyme (ACE) inhibitors. The analysis from the SHIFT trial assessed the efficacy of ivabradine in patients with different baseline levels of SBP.31 The results of this analysis demonstrated that baseline SBP did not affect the impact of HR reduction with ivabradine on clinical outcomes in HF. There was a similar beneficial effect on both the primary composite end point of CV mortality or hospitalization for HF and on the selected secondary end points whatever the baseline SBP, including patients in the low-SBP group (<115 mm Hg). The safety profile of ivabradine was also similar in the 3 groups, and there was no difference compared with the global SHIFT population. The BP variation over 24 months was similar in ivabradine- and placebo-treated patients in the low-SBP group.

**Patients with diabetes mellitus**
Recent analysis from the European Society of Cardiology (ESC) Heart Failure Pilot Survey demonstrated that 29% of patients with HF have diabetes mellitus (DM), which was independently associated with a higher risk of mortality and/or HF hospitalization.32 The preliminary data reported at the last European HF congress showed that 31% of patients with DM enrolled in SHIFT showed similar benefits from ivabradine in patients with or without DM.33 The RR of the primary composite end point of CV mortality or hospitalization for HF was decreased significantly by ivabradine in both groups: by 19% (P=0.012) in patients with DM and by 17% (P=0.002) in patients without. There was no significant difference in the impact of ivabradine in the 2 groups (P for interaction=0.864). The RR of HF hospitalization was reduced similarly by ivabradine in patients with (27%; P=0.001) or without DM (17%; P<0.001) (P for interaction=0.784).

**Elderly patients**
The analysis from the SHIFT trial demonstrated that age does not limit the benefits of ivabradine in patients with chronic HF and systolic dysfunction, with comparable safety and efficacy across all age groups.34 In a subgroup of 722 very elderly patients aged at least 75 years, end points also occurred less frequently with ivabradine than with placebo. The rate of CV deaths was lower (16% vs 22%; P=0.048), as was the rate of HF death (4% vs 8%; P=0.019).

**Good tolerability profile and ease of use in practice**
Ivabradine was well tolerated in patients with CHF. In the SHIFT trial, bradycardia led to study withdrawal in only 1% of the overall population, which is remarkable considering that 89% were receiving β-blockers.15 Based on the SHIFT trial, a starting dosage of 5 mg twice daily is recommended, and can be increased up to 7.5 mg twice daily according to tolerability and if resting HR is above 60 bpm. In patients aged 75 years or more, a lower starting dosage should be considered (2.5 mg twice daily with further titration if necessary). Ivabradine should not be used with moderate or strong cytochrome P450 3A4 (CYP3A4) inhibitors.

Due to its pharmacological properties and supported by clinical evidence, ivabradine is a particularly pertinent therapy to achieve all treatment targets in HF patients: the improvement of symptoms, well-being, and outcomes. Pharmacological
therapy of HF patients is becoming increasingly complex as patients are older and increasingly develop noncardiac and CV comorbidities and disabilities. These conditions not only complicate the management of HF patients, but also increase the risk of in-hospital and postdischarge mortality and morbidity. The efficacy and tolerability of ivabradine in patients with HF and different clinical profiles (elderly, severe disease, low BP, presence of comorbidities including renal dysfunction, DM, COPD) make ivabradine an essential therapeutic modality for the management of patients with HF.

References


Autrefois pathologie relativement brève, rapidement mortelle, l’insuffisance cardiaque systolique (IC) est aujourd’hui une maladie chronique caractérisée par des événements récurrents non mortels (hospitalisations). La charge des hospitalisations pour IC étant croissante, la prévention des réhospitalisations devient le besoin le plus urgent en cardiologie. La sortie de l’hôpital est un moment privilégié pour identifier les facteurs pronostiques modifiables et optimiser le traitement du patient. Le profil clinique des patients IC est complexe, principalement en raison de l’âge et de la présence fréquente de comorbidités cardiovasculaires et non cardiovasculaires qui, non seulement compliquent la prise en charge des patients IC mais aussi augmentent le risque de morbi-mortalité à l’hôpital et à la sortie de l’hôpital. Le rôle important de Procoralan (ivabradine) dans la prise en charge des patients atteints d’IC chronique est bien établi et conforté par ses effets bénéfiques dans la prévention de la morbidité et de la mortalité. L’efficacité et la tolérabilité de l’ivabradine chez les patients IC, y compris ceux aux profils cliniques différents (sujet âgé, maladie grave, pression artérielle basse, comorbidités dont une dysfonction rénale, un diabète, une bronchopneumopathie chronique obstructive), en font un traitement particulièrement pertinent de l’IC sous tous ses critères, dont l’amélioration des symptômes et du bien-être comme des résultats. C’est la promesse d’un meilleur pronostic et d’une qualité de vie améliorée pour des millions de patients souffrant d’IC chronique.
Improving patient competencies through therapeutic education of patients, relatives, and caregivers is a key point in heart failure (HF) management. It can be considered the first step toward a real partnership between healthcare professionals and patients. Despite all guidelines, recommendations, and convincing evidence, HF therapeutic education is rarely implemented, which may contribute in large part to the inefficacy of therapy and the overuse of emergency department facilities by poorly involved and -informed patients. In real life, it is difficult to improve patient self-management because of its dependency on patient willingness and due to the lack of time that healthcare professionals in most countries can invest in such an endeavor. However, HF therapeutic education tools are very useful, helping doctors, nurses, dieticians, and physiotherapists to quickly develop patients’ skills and competencies that improve life with the disease. This is especially pertinent in HF, due to the 5-day delay between the emergence of clinical signs and hospital admission in the majority of patients. Such tools should be flexible and adaptable to the healthcare professional and patient type, with different tools possibly more suitable for different situations. Such tools should not be stressing, but realistic, fostering autonomy in patients and their relatives. Some tools already exist, helping nurses and doctors train patients in difficult environments while facing time constraints. Try these tools or create your own to help your patients improve their everyday life with chronic HF.

**Interview with P. Jourdain, France**

Compliance is not the lone determinant of patients’ involvement in their own medical disease management. While compliance is mandatory, it is in itself insufficient. The concept of therapeutic patient education includes an improvement in patient knowledge and in patient involvement in follow-up (identification of symptoms; identification of warning signs; analysis of usual biochemistry results...). However, the crucial point is the patient’s capacity to be involved in self-management.”

**In heart failure today, what are some of the challenges to optimal management?**

Heart failure (HF) is a severe chronic condition. Management of chronic HF implies an adaptation of daily life, salt consumption, and physical activity and also involves many different medications. Furthermore, there are many issues that contribute to the nonoptimal HF management seen in real life. Some are patient related, involving for example therapy adherence or comorbidities, and some are doctor related, such as medical inertia.

Compliance with medical therapy is crucial to therapy effectiveness, as shown in a post hoc analysis of the CHARM study (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity). In this study, poor compliance, defined as the intake of less than 80% of prescribed protocol therapy, was associated with an
increase in risk of death or HF rehospitalization. Poor compliance is common in real life, especially in the oldest patients with many comorbidities and more than 5 different therapies. The difference between prescribed therapy and actual intake of therapy is often underestimated by doctors, despite the number of publications attesting to this discrepancy. This is particularly well analyzed in non–insulin-dependent diabetic patients. In those patients, a study determined that patients receiving a combination of 2 drugs (sulfamid and metformin) received only 266 days of therapy per year. This lack of compliance is comparable in chronic severe cardiac diseases such as myocardial infarction and HF. For example, 1 month after acute myocardial infarction, one-third of the patients have stopped at least 1 of the recommended BASI therapies (β-blockers, aspirin, statins, and angiotensin-converting enzyme inhibitors).

What influences compliance with medical therapy and how can it be improved?

Determinants of compliance differ greatly from patient to patient. Some are related to the therapy itself: form, taste, texture, name of medication, and side effects (real or not). Some are related to the patient: social and financial autonomy, dementia, perception of the disease and the usefulness of medical therapy, clinical evidence of usefulness, etc. Some are related to doctors: level of support of therapy (strong or weak) and the link between pharmacist and doctor. Compliance is mainly based on the confidence among doctors, pharmacists, and patients and is mandatory for an effective medical therapy. Considering optimal therapy to mean 100% compliance, a mean compliance higher than 80% is acceptable according to most publications. Improving compliance is a crucial, but difficult, target in everyday practice. The first step is to systematically analyze compliance during the medical visit. Rather than asking directly, it is more effective to ask patients indirectly how they analyze the impact of their therapy, what they are doing to avoid forgetting to take their tablets, etc. Most of the tools proposed to patients are based on tablet boxes and on connected tablet boxes (eg, they can ring phones to send reminders, are connected to the Internet, or can send e-mails to relatives), an approach to medical therapy focusing on close surveillance, which can seem intrusive. Though the short-term impact may be positive, the advantage in the long term is questionable.

Are there other ways to improve HF management through active involvement of the patient?

Indeed, compliance is not the lone determinant of patients’ involvement in their own medical disease management. While compliance is mandatory, it is in itself insufficient. The concept of therapeutic patient education (TPE) includes an improvement in patient knowledge and in patient involvement in follow-up (identification of symptoms; identification of warning signs; analysis of usual biochemistry results, eg, renal function, natremia, kalema, and sometimes natriuretic peptides). However, the crucial point is the patient’s capacity to be involved in self-management. This self-management can be split into 2 different dimensions. One is more focused on patient ability to identify the risk of decompensation (analyzing clinical signs) and to contact the general practitioner or the cardiologist rather than going later on to the emergency department. The second dimension is focused more on self-medication and adaptation of diuretic therapy, which diabetics are doing with insulin. Involving patients not only in regards to compliance with medical therapy, but also in everyday follow-up or management is crucial and substantially changes the relationship between patients and doctors. This cooperation implies that the patient takes on the role of equal partner and is no longer only a patient, signifying that the patient and relatives can play an active role in daily follow-up.

How do we reach this “partnership” between patient and health care professional?

In order to obtain this “holy grail,” it is first necessary to train patients and to improve their reactivity, not only their knowledge. Take as an example, the driving of a car. To be able to drive that car, one must first learn the road code. However, that isn’t enough to drive safely; the driver must practice and learn to adapt trajectory and speed to the environment. In HF, patients need to adapt their alimentation and their reactions to the disease, their clinical signs, and to the health resources available. TPE regroups all these concepts and has proven its effectiveness to limit hospitalization, duration of stay, and even all-cause mortality in meta-analysis and in real-life analysis in France. European Society of Cardiology (ESC) guidelines and US guidelines recommend to the highest degree multidisciplinary TPE due to its impact on patient health and on health resource expenditures. Despite all guidelines and evidence-based medicine, TPE is actually only carried out with few patients in real life (eg, estimated to be 5% in France) and is highly dependent on the motivation of local health professionals, thus not implemented equally in all places. Some specific tools are already in existence and are extremely useful to encourage doctors and nurses and to provide support to local teams and patient associations.

What are the important characteristics of these kinds of tools?

TPE tools or systems should be:

◆ Simple. The system should be easily understood by health care professionals. Its concept and use should be as near as possible to what is familiar in usual practice and not require long and complex explanations.

◆ Adaptive. The system should be adaptable to all medical practices. In some countries, it could be used by nurses and
therapeutic patient education

Therapeutic education: which tool for whom? – Jourdain

The type of tool depends on the goal defined at the beginning of the educational process, be it improving compliance, knowledge, or self-management.

◆ Improving compliance. For this goal, we have 2 main options. One focuses on patient follow-up and is related to warning systems (eg, connected watch, smartphones, short message service [SMS], e-mails), but could be based on non-numerical systems (eg, sticky notes, a diary, posters on the fridge). The second one focuses more on patient motivation and is based on the patient's perception of the benefit/risk ratio of taking his/her tablets. Remember that from a patient's point of view, a side effect is certain and has a short-term perspective, while therapy benefit is uncertain and has a long-term perspective. TPE improves compliance and motivates the patients to take all their medical therapy during all their life. Proactive patients could themselves indicate their compliance, using simple declarative tools (eg, on a smartphone, similar to patient medical passports). It is easy to estimate patient motivation in the first month using this type of tool, but it is difficult to maintain this kind of self-estimation every day for years.

◆ Improving knowledge. Information for patients is sometimes scarce and leads to extensive use of the Internet in search of “clear” information about their disease or lifestyle modifications it imposes. However, they may also find confusing or false information in this manner. The more we provide correct and useful information about daily life with their disease, the less inclined patients will be to search for it elsewhere. Specific internet sites focusing on specific diseases are interesting solutions, but require the patient to access these internet sites. Another promising solution is the development of specific applications that send daily text messages to a patient’s smartphone. One such application is “MyHF,” which relays key messages based on real preoccupations of patients. If doctors are aware of these solutions, they might find them helpful to relay information from the doctor or pharmacist to the patient.

◆ Improving self-management. This is considered the main target, because it is the main objective behind equipping the patient with information. When the patient is not only informed, but also reactive and involved in his/her follow-up with the optimization of lifestyle and the awareness of what to do in case of the most frequent warning signs or complications, the patient becomes a real “nonmedical” partner.

Changing patient competencies and not only improving patient knowledge is the main objective of TPE. TPE involves a multidisciplinary team—including nurses, dieticians, doctors, and sometimes a physiotherapist—and it needs time. In real life, few patients benefit from TPE (less than 5% in France, for example), despite its being highly recommended in all international guidelines. The 2 mandatory elements are (i) an educational diagnostic at the beginning of TPE in order to adapt the program to the patient’s current knowledge and perception of the disease and to the therapy and (ii) the setting of a common goal, together with the patient, for the next visit (improvement of lifestyle, improvement in ability to identify warning signs, improvement of follow-up, etc). Aside from these 2 elements there are different tools that could be helpful. Some focus on serious games (Internet, apps, gamepads, etc). These serious games appear to be dynamic, are “real-life” based and interactive, but are costly and have low flexibility for the patients. Some focus on “real-life” clinical cases or may be board games like the HF toolbox game now avail-
able in 32 countries with the help of a Servier partnership. These are more adaptive to the entire spectrum of patient ages and available health care resources (no need for Internet or computer access). This is particularly pertinent in HF due to the old age of patients (≈78 years old in Europe). The tools have to adapt to the patient, not vice versa.

Who should TPE be offered to and when?

Information should be given to all patients and their relatives regardless of age and social status. TPE is crucial at the beginning of the disease especially for less-involved or -informed patients. Using relaying tools like the MyHF app or using diaries could be helpful to maintain patient motivation and compliance. The tools should be adapted to a patient’s limitations (visual, hearing, age, comorbidities, etc), but all patients except those that refuse should be included in local or national self-management programs.

**Keywords:** compliance; heart failure; knowledge; self-management; therapeutic patient education

---

**Any final comments on incorporating TPE into HF management?**

To sum up, optimal management of HF should include TPE to improve patient knowledge, compliance, and reactivity, and such initiatives are enhanced using adapted tools. These tools have to be flexible and adjusted to each patient’s level of motivation, beliefs, and limitations. All these tools should be adapted to local key messages and health care resources. These tools already exist and could support the deployment of education programs. Therapeutic education is not simply education, but is intrinsically a therapeutic act, which we propose to the patient as we would medical therapy or device treatment. Indeed, TPE is changing how patients see themselves: from obedient patients to active lifelong partners. It is also changing the doctor’s relation with the patient, with the doctor becoming an ever more attentive caregiver.

---

**L’ÉDUCATION THÉRAPEUTIQUE : QUEL OUTIL ET POUR QUI ?**

L’amélioration des compétences du patient par son éducation thérapeutique, celle de ses proches et des soignants est un point clé de la prise en charge de l’insuffisance cardiaque (IC). C’est la première étape vers un véritable partenariat entre les professionnels de santé et les patients. Malgré toutes les directives, recommandations et données convaincantes, l’éducation thérapeutique de l’IC est rarement mise en œuvre, ce qui contribue en grande partie à l’inefficacité du traitement et à la sur-utilisation des services d’urgence par des patients mal informés et peu impliqués. Il est difficile dans la vraie vie d’améliorer l’auto-prise en charge du patient, car elle dépend de son bon vouloir et, dans la plupart des pays, du manque de temps que les professionnels de santé peuvent investir dans un tel effort. Cependant, les outils d’éducation thérapeutique de l’IC sont très utiles, aidant les médecins, les infirmières, les diététiciens et leur kinésithérapeutes à développer rapidement les compétences et les capacités des patients pour mieux vivre avec la maladie. C’est particulièrement vrai dans l’IC, à cause du délai de 5 jours entre la survenue des signes cliniques et l’hospitalisation chez la majorité des patients. Ces outils doivent être flexibles et adaptables aux professionnels de santé et au type de patients, avec des outils probablement plus adaptés à différentes situations. Ces outils ne doivent pas être source de tension mais réalisés, encourageant l’autonomie des patients et de leurs proches. Des outils existent déjà, aidant infirmières et médecins à former les patients dans des environnements difficiles, tout en faisant face à des contraintes de temps. Essayez-les ou créez les vôtres pour aider vos patients à améliorer leur vie quotidienne avec une IC chronique.
Challenges in predicting heart failure readmission: focus on heart rate

by M. Böhm, Germany

Chronic heart failure is characterized by a high readmission rate, in particular in patients with advanced syndrome. Shortly after discharge, neuroendocrine activation is particularly evident, resulting in elevated heart rate and low blood pressure. Both of these vital signs are closely associated with high morbidity and mortality. The open question is whether early treatment to achieve heart rate reduction with an If-channel inhibitor like ivabradine could reduce the high readmission rate. As heart rate is associated with hospital admissions and mortality, this approach is worthwhile to study in a prospectively randomized trial.

Despite intensive multidrug therapy, patients with heart failure are often readmitted to hospital, resulting in an annual rehospitalization rate for heart failure in the United States of 1 million patients per year.1 Despite evidence-based treatments, often initiated in the hospital, these individuals face high postdischarge mortality and rehospitalization rates: 15% and 30%, respectively, within 60 to 90 days.2-4 Mechanistically, during this vulnerable phase, an excess of neuroendocrine activation likely contributes to the high event rate. To take one example, the escape phenomenon of the renin-angiotensin-aldosterone system (RAAS) provides the basis for a combined inhibitor therapy for heart failure5-7 in stable patients, but such therapy during the postdischarge vulnerable phase has failed to show benefits.8,9 The treatment of these patients is limited due to the fact that they quite often have low blood pressure and high heart rates, preventing physicians from treating with adequate doses of neuroendocrine antagonists.10

Association of heart rate and blood pressure

Elevated heart rates in heart failure increase oxygen consumption11 and might reduce cardiac contractility due to the inverse force-frequency relationship in vitro12,13 and in vivo.14 In patients with stable heart failure with a heart rate above 70 beats per minute (bpm) included in the SHIFT trial (Systolic Heart failure treatment with the I_R inhibitor ivabradine Trial), heart rate was associated with an increased risk of cardiovascular death and heart failure hospitalizations,15 which translates into a 3% increase in risk for every 1-bpm increase from baseline heart rate and 15% increase in risk for every 5-bpm increase. Consistently, heart rate reduction with ivabradine in stable patients with heart failure was able to reduce the composite outcome of cardiovascular death and heart failure hospitalization in individuals with a heart rate above 70 bpm16 and even cardiovascular death and total mortality in the subgroup.
of patients with a heart rate above 70 bpm. For the postdischarge phase, there are no data on treatment effects of heart rate reduction. However, a substudy for the EVEREST trial (Efficacy of Vasopressin antagonism in hEart failuRE: outcome Study with Tolvaptan) has shown that early after discharge, a heart rate above 75 bpm was associated with an increase in mortality, while heart rate at admission showed no association (Figure 1). Furthermore, in a large hospital registry, the threshold heart rate for an increased risk was 70 to 80 bpm in determining 30-day and 1-year cardiovascular death. This observation provides the basis for the hypothesis that heart rate reduction early after discharge might improve outcome. However, this has to be closely examined in prospective randomized trials.

After discharge from heart failure hospitalization, undertreatment of patients with β-blockers and angiotensin-converting enzyme (ACE) inhibitors occurs—in particular, in high-risk patients with presumably low blood pressure (Figure 2) and this does not change over the year following discharge.

Therefore, early initiation (even in hospital) of heart rate-reducing therapies such as ivabradine, which is not accompanied by blood pressure reduction, might lead to a higher proportion of patients receiving evidence-based treatment, which includes heart rate reduction, in the year after discharge. In the long run, this could improve outcomes.

Heart rate–reducing therapy after discharge

The problem in the treatment of the postdischarge vulnerable patient is that about 15% to 25% of patients present with low blood pressure (ie, <120 mm Hg), which puts them at a particularly high risk for poor outcomes. Interestingly, in SHIFT, high heart rates and low blood pressure, in particular the combination thereof, further increased event rates in heart failure patients. In this heart failure population at particularly high risk, the heart rate reducer ivabradine showed no heterogeneity of treatment effects whether blood pressure was low or high. Furthermore, ivabradine treatment in stable patients did not reduce blood pressure, but even slightly increased it. Patients with low blood pressure are more likely to suffer from multiple cardiovascular and noncardiovascular comorbidities. In the SOLVD (Studies Of Left Ventricular Dysfunction) population, the cumulative load of comorbidities was accompanied by a strong increase in cardiovascular morbidity and mortality. Also, in SHIFT, there was no heterogeneity of the treatment effects in the elderly, in patients with particularly severe heart failure or low ejection fraction, impairment of renal function, intensive treatment with mineralocorticoid antagonists, chronic obstructive pulmonary disease, or left bundle branch block.
Though still to be proven whether heart rate reduction is safe in this condition, in the critically ill patient, like in patients with multiple organ dysfunction syndrome, high heart rate was related to poor outcome. Thus, one ongoing trial is looking at the effect of heart rate reduction with ivabradine in septic shock. The association of heart rate and outcome also holds true in acutely admitted patients with hypertensive crisis.

Early experiences with patients in cardiogenic shock provide evidence that this drug has potential to be applicable in critical cardiac disease and, thus, also in patients in a fragile postdischarge situation. Again, the treatment effect from lowering heart rate has to be carefully examined in prospective randomized trials to validate these hypotheses-generating associations.

**Perspectives and future research**

While the effect of heart rate reduction is established and such treatment has been introduced in the heart failure guidelines of the European Society of Cardiology in stable heart failure patients, data on the postdischarge situation are not available. Reduction in rehospitalization for heart failure is a crucial goal in heart failure treatment, because hospitalizations markedly worsen the prognosis in heart failure patients. Interestingly, ivabradine was shown not only to reduce those heart failure hospitalizations occurring as first events, but also recurrent hospitalizations, with a similar risk reduction as for first events for patients on ivabradine compared with placebo. Thus, a prospective trial in postdischarge patients is needed to show whether heart rate reduction—in particular, in vulnerable patients with low blood pressure early after discharge, in the context of guideline-based therapies for heart failure—might improve clinical outcomes in patients with this disabling condition.

**Practical considerations**

Despite some deficits in scientific knowledge, heart rate measurement is a very simple tool to predict future outcomes in chronic heart failure patients. Since heart rate is related to cardiovascular death and heart failure hospitalization in stable patients, it is also predictive of outcome early at discharge. Heart rate is also closely associated with symptoms, being in turn associated with outcomes.

Therefore, the determination of heart rate in accordance with well-being of the patients at discharge might provide important information helping clinicians to identify those at high risk for future complications. Those patients would require special attention, such as up titration of the doses of heart failure medications and initiation of ivabradine to reduce heart rate when heart rate stays above 70 bpm. Heart rate should be calculated as in clinical trials, by an electrocardiogram (ECG) following sufficient rest time and, as recommended by guidelines, in the sitting position, counting heart beats for 30 seconds and then multiplying the value by 2. Altogether, high heart rate has been identified as a risk marker and in heart failure has been determined to be a modifiable risk factor for outcomes that are amenable to heart rate-reducing therapy. In chronic heart failure, the normal or beneficial heart rate is to be newly defined as below 70 bpm.

---

**References**

Focus


35. McMurray JJ, Adamopoulos S, Anker SD, et al; Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Soci-ety of Cardiology, ESC Committee for Practice Guidelines, ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012;14:803-869.


Keywords: heart failure; heart rate reduction; i-channel inhibitor; ivabradine; postdischarge; rehospitalization
L’insuffisance cardiaque chronique se caractérise par un taux élevé de réhospitalisation, surtout pour les patients à un stade avancé. L’activation neuro-endocrinienne est particulièrement évidente juste après la sortie de l’hôpital, se manifestant par une fréquence cardiaque élevée et une pression artérielle basse. Ces deux signes vitaux sont étroitement associés à une mortalité et une morbidité élevées. Reste à savoir si un traitement précoce pour diminuer la fréquence cardiaque par un inhibiteur du canal I_{f} comme l’ivabradine pourrait réduire le taux élevé de réhospitalisation. La fréquence cardiaque étant associée aux hospitalisations et à la mortalité, c’est une question qui mérite de faire l’objet d’une étude prospective randomisée.
In parallel to the increasing complexity of medical and device therapy in chronic heart failure, patients in need of treatment are growing older. Specifically in the case of deterioration of cardiac function and symptoms of heart failure, evaluation of heart failure status may differ between subjective assessment of well-being and assessment based on objective parameters. Advances in telemonitoring may offer an opportunity to help rebalance the continuously growing health economic burden. Current concepts of telemonitoring in heart failure include measurement of weight, vital signs, and concentrations of B-type natriuretic peptide, as well as changes in intrathoracic impedance and in pulmonary artery and left atrial pressures. The importance of remote monitoring in patients with cardiac implantable electronic devices is already positively addressed in current European guidelines. However, clear interpretation of studies on noninvasive telemonitoring has been hindered by non-standardized definitions of end points and by the lack of end point definitions specific enough to describe successful disease management through telemedical intervention. Although 2 meta-analyses have demonstrated an overall beneficial effect of telemedicine over usual care in patients with chronic heart failure, 2 large randomized trials did not confirm former positive results. Subsequently, today’s international guidelines do not state a clear recommendation for telemedical support. Despite these limitations, telemonitoring has the potential to improve heart failure care in various ways, most importantly by improving quality of life and by reducing cardiovascular morbidity and mortality.

Generally speaking, telecardiology is one of the most advanced fields in telemedicine. Looking back to Willem Einthoven’s first description of the successful transmission of a single-lead electrocardiogram (ECG) over a telegraph line in 1906, many decades would pass before the importance of telemonitoring in heart disease would surface again. Today, over a century later, state-of-the-art medical device technology for heart disease facilitates communication between patients and caregivers. Specifically, in the case of chronic heart failure, telemonitoring can contribute to timely diagnostic and therapeutic measures. A number of concurrent developments such as demographic change in industrialized countries and revolutionary improvements in cardiovascular diagnostics, therapy, and medical device technology—specifically in regard to hypertension and coronary heart disease in recent years—can be implicated in the clearly growing number of heart failure patients.
failure patients. Indeed, current data of the German population estimate there are more than 1.8 million inhabitants suffering from chronic heart failure. Put in other numbers, every tenth inhabitant over 65 years of age is affected and approximately 200,000 to 300,000 cases are newly diagnosed every year. Other population-based statistics such as those for the United States reveal similarly increasing numbers. In Germany alone, the cost of heart failure treatment is approximately €3 billion per year. Advances in telemonitoring of these patients may provide an opportunity to help rebalance the continuously growing health economic burden. The development of efficient and secure information/communication technology and the growing use of Internet-based platforms enable a broad spectrum of telemonitoring methods to surface. The present article reviews current concepts of telemonitoring in the field of heart failure, all carrying the potential to improve medical caregiving in various ways and thus, ideally, reducing morbidity and mortality in heart failure.

### Perspectives for telemonitoring in heart failure

#### Subjective assessment and objective surveillance parameters

Specifically in the case of deterioration of cardiac function and symptoms of heart failure, evaluation of heart failure status may differ between subjective assessment of well-being and assessment based on objective parameters. In daily practice, relying on patients’ subjective perception of clinical symptoms may therefore not be sufficiently reliable to detect cardiac decompensation at an early stage. For many of these patients, recurrent in-hospital treatment may seem unavoidable. The starting point of heart failure treatment strongly depends on the patient’s venue of “usual care.” Clinical practices and therapeutic regimens may differ between medical specialties, individual physicians, and even sexes. In addition, the accessibility of dedicated heart failure clinics and patient education activities depends on regional circumstances.

Current concepts of telemonitoring in heart failure include measurement of weight, vital signs, and concentrations of B-type natriuretic peptide, as well as changes in intrathoracic impedance and in pulmonary artery and left atrial pressures. The relationship between these objective parameters and the clinical situation, however, may be quite complex and prone to interference due to cofactors. For example, in some patients, significant weight gain may not always correlate with fluid retention or can occur slightly delayed to decompensation. Understandably, there are limits to any single parameter applied as a surrogate for imminent cardiac decompensation.

A classification of telemedicine in heart failure proposed by Anker et al in 2011 describes 4 generations of noninvasive telemonitoring strategies (Figure 1, page 204) and thus does not touch upon the use of remote monitoring via cardiac implantable electronic devices.

#### Appropriate end point definitions in telemonitoring studies

Current studies on heart failure management with use of telemonitoring are discussed in detail further below. So far, clear interpretation of these studies has been hindered by nonstandardized end point definitions and by the lack of those specific enough to describe successful disease management through telemedical intervention. Undoubtedly, frequent hospitalizations are a relevant health economic burden and inhospital care due to heart failure is an important marker of disease deterioration. However, counting hospital admissions in order to measure clinical success of telemonitoring may not accurately reflect the whole situation.

The primary choice of applicable end points and the appropriate interpretation of study results depend largely on the design and duration of the individual study. Contemporary time-to-event outcome analysis can therefore be misleading. Indeed, an analysis of time to first hospitalization for heart failure or cardiovascular death would suggest that a patient who had an early, short rehospitalization and perhaps no further hospitalization afterwards would have a worse outcome than a patient who died just some time later, which is clearly not the case. Hence, novel methods of comparison carrying the potential to reveal the true impact of hospitalization on the clinical status of heart failure patients are warranted. It is conceivable that patients who receive telemonitoring or other measures of intensified care may even be hospitalized more often, though quite possibly in a less symptomatic stage and ideally with a shorter length of stay than patients who are hospitalized acutely in a very critical situation.
Clinical studies for noninvasive use of telemedicine in heart failure

In 2005, the TEN-HMS study (Trans-European Network – Home-Care Management System) was the first larger study that analyzed the role of telemonitoring in selected patients with heart failure.² TEN-HMS was a 3-arm, prospective randomized study in which patients included had a recent admission for heart failure, a left ventricular ejection fraction (LVEF) under 40%, persisting symptoms of heart failure, the need for diuretic therapy, and at least 1 predefined additional marker of higher risk, such as an LVEF under 25% or treatment with furosemide at a dosage of greater than or equal to 100 mg/day. In total, 426 patients were assigned randomly to telemonitoring, nurse telephone support, or usual care in a 2:2:1 ratio.

Telemonitoring enabled data transfer (weight, blood pressure, ECG) via a conventional telephone line to a central Web server and then via secure intranet connections to a workstation based at each investigator site. Patients were asked to transfer data twice daily. Values greater than or less than prede-
fined limits were signaled automatically to study nurses who could provide advice to the patient directly or, in more severe cases, first inform the primary care physician.

In addition to usual care, patients in the group with nurse telephone support were able to contact the heart failure-specialist nurse by telephone at any time during office hours. Additionally, the nurse contacted the patients by telephone each month in order to assess their symptoms and current medication and to provide advice. In comparison with usual care alone, mortality and rehospitalization rates were lower in the groups receiving either telemonitoring or nurse telephone support, with no significant differences between both these intervention groups. Of note, the duration of hospital stay and therefore the time until outpatient care was sufficient was 6 days shorter in the group of patients receiving telemonitoring.

A number of other studies, such as HOME-HF (Evaluation of Patients With Heart Failure Using Home Telemonitoring) and HHH (Home or Hospital in Heart failure) have described similar benefits of telemonitoring in heart failure in regard to the frequency and duration of hospitalizations and contacts with emergency services due to recurrent decompensation.

Bringing together the available data, 2 meta-analyses demonstrated an overall beneficial effect of teleremedical intervention over usual care in patients with chronic heart failure. A Cochrane Collaboration meta-analysis published in 2011 described the advantage of telemonitoring in heart failure in respect to reducing overall mortality by 44% and hospitalizations by 21%. However, the variable methodological quality between studies and small study populations limited data interpretation.

In contrast, 2 large, prospective randomized trials: Tele-HF (Telemonitoring to improve Heart Failure outcomes) and TIM-HF (Telemede Interventional Management in Heart Failure) did not confirm former positive results.

Tele-HF randomized 1653 patients to either telemonitoring with use of a commercially available system (Tel-Assurance, Pharos Innovations, USA) or usual care. Telemonitoring operated on the basis of toll-free calls to an interactive voice response system that questioned general health, heart failure symptoms, and body weight daily and signs of depression once a month. Clinicians reviewed patients’ answers on business days and patients whose data indicated worsening of heart failure were contacted. Individual contact with nurses or doctors by telephone was not provided. In Tele-HF, telemonitoring with use of the automated Tel-Assurance did not improve outcomes. The primary end point defined as all-cause hospital readmission or death within 180 days was achieved in a comparably high number of patients (52.3% in the telemonitoring group and 51.5% in the group receiving usual care; \( P=0.75 \)). Furthermore, death rates did not differ between groups.

The TIM-HF trial equally randomized 710 patients suffering from heart failure in New York Heart Association (NYHA) functional class II or III and an ejection fraction less than or equal to 35% to 2 groups—the first receiving usual care and the second receiving a portable device with which they could transfer data on weight, blood pressure, and ECG via Bluetooth to a telemedical service center. In comparison with earlier concepts, the telemedical center provided physician-led medical support 24 hours per day, 7 days per week for the entire study period. Furthermore, the telemedical center contacted the patient’s local physician at least every 3 months and an emergency system was integrated in accordance with standard operating procedures. Follow-up duration was 12 months minimum; mean follow-up was 26 months. All-cause mortality constituted the primary outcome. The main secondary outcome measure was cardiovascular death or hospitalization due to worsening of heart failure. Patients in both study arms had optimized medical therapy (angiotensin-convert-}

ző 

ing enzyme [ACE] inhibitors, 96.6% versus 94.1%; \( \beta \)-blockers, 92.3% versus 93.0%; aldosterone antagonists, 65.3% versus 63.2% in the usual care group versus the telemonitoring group, respectively). Compliance with daily data transfers was high (>70%). In regard to the primary and secondary outcome measures, no significant effect of telemonitoring was detected.

To summarize the 2 aforementioned trials, in comparison with usual care and medical therapy, both randomized studies were unable to detect a significant reduction in all-cause mortality or rehospitalization in the group receiving telermede intervention as an adjunct to usual care. However, the study design and population of both trials require critical analysis. In the Tele-HF trial, the concept of data transfer for weight and symptoms to an automated speech recognition system was hardly made use of by most study patients and in itself does not represent today’s perception of telermedical care. For the case of the TIM-HF trial, body weight, blood pressure, and a 3-lead ECG were transmitted on a daily basis; however, requirement for study patient enrolment included fully optimized and guidelines-adherent therapy before initiation of telermonitoring. The high percentage of patients with implantable cardioverter defibrillators (>40%) may be reflected in the low mortality rate (~8% per year) in this study as well. Unfortunately, such pronouncedly optimized drug and device therapy in patients who additionally were cared for by a cardiologist every 3 months, as in the TIM-HF study, does not reflect “real-world” medical care in heart failure. This preoptimized situation may, however, explain why the TIM-HF study did not reveal an additional benefit of telermonitoring and the very low occurrence of end points in the overall cohort. Subgroup analysis showed a significant benefit of telermonitoring in certain cohorts, such as those patients who suffered decompensated heart failure in the past. These promising results in subgroups lead to the initiation of the TIM-HF II study (Telemedical Inter-
Implantable sensors

Novel concepts to measure physiological signs of disease progression, such as increasing pulmonary artery pressures measured directly with implantable monitors, may complement the current strategy of external, remote telemonitoring. In the CHAMPION trial (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Patients), tailored therapy according to pulmonary artery pressures was associated with a 39% reduction in heart failure hospitalizations. Furthermore, the HOMEOSTASIS study (Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients) described improved hemodynamics, sympotms, and outcomes in patients at high risk for recurrent decompensation who, in addition to usual care and under guidance from a heart failure team, self-adjusted their diuretic therapy according to the measurements of an implanted left atrial pressure sensor.

Timely prognostication of upcoming decompensation may also be provided by certain cardiac resynchronization therapy defibrillator (CRT-D) devices, which also have the functionality to monitor fluid index and patient activity. In the PARTNERS HF study (Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure), a combined algorithm was used to detect which patients of the 694 included fulfilled predefined criteria for higher risk. The criteria included long atrial fibrillation duration, rapid ventricular rate during atrial fibrillation, high fluid index, low patient activity, abnormal autonotics (increased heart rate at night or low heart rate variability), and device therapy. The algorithm required at least 2 abnormal parameters to be considered positive. The results revealed that those patients who had positive combined heart failure device diagnostics had a 5.5-fold increased risk of heart failure hospitalization with pulmonary signs or symptoms within the next month. Thus, the study suggested that regarding subsequent events, diagnostics driven by CRT-D device data may stratify heart failure patients into high- and low-risk groups.

Guideline recommendations

Due to sufficient evidence available, the importance of remote monitoring in patients with cardiac implantable electronic devices is already positively addressed in current European guidelines (European Society of Cardiology [ESC] class IIa, Level A). Of note, this current article focuses on the use of non-invasive telemonitoring techniques in heart failure. According to the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) 2009 and 2013 heart failure guidelines, postdischarge systems of care, such as telecommunication, should be used to support the transition to effective outpatient care. However, the American guidelines summarize current evidence for the individual components of heart failure management such as home-based care, disease management, and remote telemonitoring programs as mixed and comment that the quality and cost-effectiveness of such programs require further evaluation. Similarly, though acknowledging the data from a meta-analysis of randomized controlled trials supporting the reduction in hospitalizations, the ESC/ESC-Heart Failure Association (ESC-HFA) guidelines do not state a clear recommendation for telemedical support. The European guidelines argue that only a few individual randomized controlled trials have shown this benefit, and thus the evidence is not robust enough to support a guideline recommendation.

Conclusion

While the complexity of medical and device therapy in chronic heart failure is increasing, patients in need of treatment are also growing older. Contemporary evaluation measures often fail to early identify those critical heart failure patients at risk for worsening of heart failure. Hospitalization is therefore common after heart failure diagnosis. The economic burden is not limited to the cost of health care services and medications, but includes lost productivity of patients and family caregivers as well. These developments may lead to difficulties in the optimal implementation of guideline specifications in daily practice. Individualized patient care seems, therefore, inevitable. From these aspects, telemonitoring may be beneficial in both the acute posthospitalization, or “bridge-to-stability” phase, and in long-term care in order to establish close and lasting control of clinical stability. Numerous nonstandardized definitions including those that have defined the specific elements of telemonitoring and optimal patient cohorts in need of support and those that have defined clinical success have been the main limitations so far. This issue has subsequently made the appropriate interpretation of data and the transfer to guideline recommendations difficult. Despite these limitations, current data point toward the potential of telemonitoring to improve heart failure care in various ways, most importantly by improving quality of life and by reducing cardiovascular morbidity and mortality.
LA TÉLÉSURVEILLANCE DANS LA PRISE EN CHARGE DE L’INSUFFISANCE CARDIAQUE :
QUE FAUT-IL POUR L’ADAPTER À LA PRATIQUE QUOTIDIENNE ?

Parallèle à la complexité croissante des traitements médicaux et instrumentaux de l’insuffisance cardiaque, les patients qui en ont besoin vieillissent. L’évaluation de l’insuffisance cardiaque peut varier entre une estimation subjective du bien-être et celle de paramètres objectifs, surtout en cas de détérioration de la fonction cardiaque et des symptômes d’insuffisance cardiaque. Les progrès de la télésurveillance peuvent aider à rééquilibrer le poids économique sans cesse croissant de la santé. La mesure du poids, les signes vitaux et les concentrations de peptide natriürétique de type B, ainsi que les modifications de l’impédance intrathoracique et des pressions artérielle pulmonaire et auriculaire gauche sont les concepts actuels de la télésurveillance dans l’insuffisance cardiaque. Les recommandations européennes actuelles prennent déjà en charge de façon positive l’importance du contrôle à distance des patients porteurs de dispositifs électroniques implantables cardiaques. Cependant, le manque de définition assez spécifique des critères pour décrire une prise en charge réussie de la maladie grâce à une intervention télémedicale et leur non-standardisation ont empêché une interprétation claire des études de télésurveillance non invasive. Deux méta-analyses ont démontré un effet global bénéfique de la télémedecine pour les soins courants des patients insuffisants cardiaques chroniques, mais deux grandes études randomisées n’ont pas confirmé de résultats positifs. Les recommandations internationales d’aujourd’hui n’ont pas présenté par la suite de directives claires pour l’assistance télémedicale. Malgré ces limites, la télésurveillance permet d’adapter différentes façons les soins de l’insuffisance cardiaque, surtout en améliorant la qualité de vie et en diminuant la morbidité et la mortalité cardiovasculaires.

References
17. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012;14(8):803-869.

Keywords: chronic heart failure; device therapy; therapy optimization
Throughout the history of the Mediterranean region of France, two cities have shone with particularly intense light: Marseille, an offshoot of Greco-Roman culture, and Montpellier, founded in the Middle Ages. Mediterranean cultural heritage past and present is now showcased in today’s vibrant Marseille in the Museum of European and Mediterranean Civilizations (MuCEM), and Montpellier, the seat of the oldest medical faculty in Europe, remains to this day a torchbearer of French medical science and clinical excellence.

MuCEM, the pride of Marseille

M. Raive, France

The Medical Faculty of Montpellier: one thousand years of medicine

C. Régnier, France
Museum of European Civilization and the Mediterranean (MuCEM):
Lattice, Bridge to Fort Saint-Jean—a jewel set against the blue Mediterranean sky and waters.
© Edmund Sumner/VIEW/Corbis.
Like a majestic black vessel poised between land and sea, the Musée des civilisations de l’Europe et de la Méditerranée (MuCEM) stands at the entrance to the port of Marseille. A perfect square girded by concrete latticework redolent of Islamic mashrabiya, MuCEM was inaugurated in June 2013, one of the few provincial museums opened in France in recent times. Designed by Rudy Ricciotti, a 62-year-old Algerian-born French architect, MuCEM draws visitors from around the world. From Marseille too, because this cultural institution is also a place where locals can stroll along walkways between the historic quarter of the upper part of town and the waterfront, taking ownership as it were of their Mediterranean port and city, founded in 600 BC by Greeks from Phocaea (Anatolia in present-day Turkey). Through its focus on society, MuCEM has from its inauguration curated high-level and thought-provoking exhibitions from sundry collections of popular art (250 000 objects and hundreds of thousands of documents) inherited from the former Musée National des Arts et Traditions Populaires in Paris: great artworks and archaeological treasures, contemporary art alongside 19th-century agricultural tools, traditional costumes from all over Europe, a fine collection of merry-go-rounds, and their wooden horses. Through a multidisciplinary dialogue between cultures and continents, MuCEM challenges us, questions us, and shows us how art is part of life.

MuCEM, the pride of Marseille

by M. Raive, France

Rarely has a contemporary building helped a townspeople take ownership of their city like the Musée des civilisations de l’Europe et de la Méditerranée (MuCEM) in Marseille. Inaugurated in June 2013, architect Rudy Ricciotti’s creation at the entrance to the port was the centerpiece of the celebrations that year when Marseille was designated European Capital of Culture. Wrapped in concrete latticework, this remarkable building, with breathtaking views across the azure of the Mediterranean, is reason enough for a stroll along its 115-meter footbridge over its encircling moats and beyond. MuCEM rose to its challenge from the outset: to attract lovers of art and architecture from around the world, but also to appeal to those for whom cultural institutions are an alien world.

France’s newest museum

What is the measure of MuCEM’s success? We need look no further than visitor numbers. In the first year after its opening, it welcomed some 950 000 visitors to its collections and exhibition rooms. Outside, over 2.8 million promenaders flocked to the

E-mail for correspondence: mraive@gmail.com
www.medicographia.com

MuCEM, the pride of Marseille – Raive
MuCEM, the Pride of Marseille.
© Edmund Sumner/VIEW/Corbis.
inclined gangways that run around the museum and on to the metal footbridge that spans the waves and joins MuCEM to the Mediterranean garden of the Fort Saint-Jean high above the port. Numbers that outstripped expectations three-fold. MuCEM, the latest museum in France and the only one inaugurated in the province for many years, is already riding high among the world’s most visited museums.

Overlooking the Mediterranean, the waterfront site blends with brio into its setting, refining it the while, such that once again it is becoming the cynosure of the Department of the Bouches-du-Rhône. To the point that for the title of the symbol of Marseille it rivals the Catholic basilica Notre-Dame-de-la-Garde, which for centuries has kept watch majestically over the city from its outcrop 150 meters above the port. Like a “Good Mother,” as it is known, the church has, since the Middles Ages, watched over Marseille’s sailors and fishermen. Expanded in the mid-19th century, Notre-Dame-de-la-Garde today stands on the site of the original small medieval chapel. The Neo-Byzantine and Romanesque styles of the church, with its square bell tower surmounted by a belfry topped by a statue of the Madonna and Child over 11 meters high, its copper gilded with gold leaf gleaming in the sunlight, contrast sharply with the harmonious and mate blacks and grays of the MuCEM. As if this crossroads of anthropology, history, archaeology, art history, and contemporary art did not wish to cast a shadow over the blue waters of the Mediterranean. MuCEM seems to hover between sea and sky. A square and sober block, enveloped by a veil of openwork concrete evocative of Islamic mashrabiyas, MuCEM’s main building (15 000 m²) has become a waterfront extension of the city on the pier from where, until decolonization, travelers from around the world came and went; jazz arrived here from the United States in the 1920s, and a decade later artists and writers fled Nazism in the other direction.

MuCEM and its rich historical setting are so stately that they seem to have become the quintessential setting for a Sunday stroll for many of Marseille’s folk, drawn as they have been since its opening by affection for this contemporary vessel, where they see, as its designer Rudy Ricciotti puts it, “the know-how of those who built it, the work of the stonemasons, engineers, site foremen, and journeymen.”

Though MuCEM “speaks to the heart of the people of Marseille,” as Ricciotti proudly relates, its attraction extends beyond the city limits. Some 85% of the visitors are French, and it is true that half of these are from the Provence-Alpes-Côte d’Azur region, but the remaining 15% are from overseas: Germany (20%), Belgium (12%), Italy (11%), Switzerland (10%), and the United States (6%). Visitors even come to Marseille with the express purpose of discovering this architectural feat.

As a great museum focused on societal issues, MuCEM houses collections transferred from the erstwhile Musée national des Arts et Traditions Populaires in Paris, created in 1937. Ethnography was MuCEM’s founding discipline, but its vocation has greater scope. Standing on the north shore of the Mediterranean, it serves as a cultural city open to the human sciences and to art in all its guises, by bringing together what is known as world culture, in a cross-cutting dialogue between the arts, cultures, and continents, between Europe, the Americas, Africa, and the Orient. By promoting exchanges between the two shores of the Mediterranean, MuCEM fulfills its calling, suggestive of the Tower of Babel or of a casbah (North African fortress) to be climbed so as to gaze across to other horizons.

How is it possible to remain untouched by the sensuous delights of this building open to the high seas at the entrance to the Old Port? By the melding of sight and touch, of odors from the sea, the taste of iodine on whistling winds from afar. Even before it was completed, Rudy Ricciotti noted that “with its aerial walkways, MuCEM conjures up the ascension of a ziggurat, a Mesopotamian terraced temple. Its membranes of dark concrete openwork evoke ties with a distant Orientalism. The south and west frontages, the sun-drenched façades of dark concrete openwork, the seawater circulating in the moats under the gangways, the smell of iodine intensified by the mistral.”

A visionary proud of his Mediterranean roots

Born in Algeria in 1952 to parents of Italian origin, raised in Provence, Rudy Ricciotti graduated from the École Nationale Supérieure d’Architecture de Marseille and is today resident in Bandol (Provence-Alpes-Côte d’Azur region). Winner of the 2006 Grand Prix national de l’architecture (“Grand National Prize of Architecture”), Ricciotti is a visionary proud of his Mediterranean roots. He loves materials rooted in the earth and in the lives of men and women. Son of a stonemason, he knows that construction is a task for men and women who dream of defying the gods and eternity. Fascinated by the “secrets transmitted by site foremen or by skilled artisans,” his enthusiasm for concrete knows no bounds. It is, he feels, a “royalty-free material easy to make from sand and cement.
MuCEM, the pride of Marseille – Raive

Gateway to the Mediterranean: MuCEM and Fort Saint-Jean, in the old harbor of Marseille, linked by a pedestrian bridge. In the background, Sainte-Marie-Majeure Cathedral. © Tim White/SOPA RF/4Corners Images/SOPA/Corbis.

Main entrance to MuCEM, at dusk. © Marc Dozier/Corbis

Display of traditional beekeeping items, early 20th century. © MuCEM. Dist. RMN-Grand Palais/image MuCEM.
anywhere on the planet.” Ricciotti loves the idea of working with concrete, which is neither “a scarce earth” nor a “speculative product.” He also lauds its complexity: “Concrete is a Mephistophelian asset, but we can make a pact with it. No one owns concrete. Nor am I a concreting architect. I don’t work concrete; it works me.” Ricciotti is a respected professional, but draws barbs from some who see in his creations, with their organic curves, the work of a mannerist, an architect out of step with the minimalism in vogue in contemporary architecture. In his own fashion, Ricciotti counters by decrying the “sensory autism” and “minimalist Salafism” of some of his more illustrious peers. He has no time for minimalism and argues for the “demuseumification” of museums.

The footbridge between the roof terrace of MuCEM and the garden of the restored Fort Saint-Jean links the revamped Boulevard du Littoral to the Panier district, the historical site of the Greek colony Massalia founded in 600 BC. A former military complex with 12th-century foundations and the square mid–15th-century Tower of René I, King of Provence, the Fort Saint-Jean was constructed in the 17th century on the site of the commandery of Saint John of Jerusalem by order of Louis XIV, to strengthen the city’s arsenal. After three centuries of military duty, the Fort Saint-Jean was severely damaged in 1944 by an accidental explosion when used by the German occupiers as an ordnance depot. A listed building since 1964, under the guardianship of the Ministry of Culture, the Fort Saint-Jean from 1970 to 2005 housed the Department for Underwater and Undersea Archaeological Research.
Fully restored to current building code standards, the Fort Saint-Jean is now open to the public for the first time, having always served as a military site, except during the French Revolution, when it was used as a prison for Philippe Egalité (name taken by Louis Philippe II, Duke of Orléans) and two of his sons, together with twenty or so Jacobins (members of the revolutionary Jacobin Club). Henceforth, visitors can explore the Tower of René I, the Salle du Corps de Garde (guardhouse room), the Officers’ Gallery, and the Saint-Jean Chapel, and discover there some of the collections inherited from the Musée National des Arts et Traditions Populaires or deposited by the National Museum of Natural History in Paris.

Within the Fort Saint-Jean, the visitor enters a world of fairgrounds and leisure activities, through a giant model of a circus with its sawdust-strewn ring, menagerie, and gallery, funfair attractions, fairground amusements and costumes, and everyday objects evoking the ages of life.

Before reaching the footbridge to the pier, a “garden of migrations” planted with white oaks, holm oaks, orange trees, myrtle, herbs, and spices has been created to illustrate, in fifteen botanical landscapes, the melding of Mediterranean cultures. The history of Marseille illustrated by the Fort Saint-Jean and the contemporary world of MuCEM are now entwined by this bridge suspended above the moats. The two sites, ancient and modern, linked by the two interwoven inclines, seem indivisible, like past and future.

Access to MuCEM along the Fort Saint-Jean footbridge, which links it to the upper slopes of town, leads to the museum roof terrace fitted out as a solarium, with a gourmet restaurant run by Gérald Passédat, a master of the herbs and vegetables of Marseille and of the fish and seafood of the Mediterranean. This terra firma overhang of a terrace juts into the sea in the shape of a perfect square 72 meters by 72. Within it, separated by winding stairs and open-air walkways, stands a smaller square, this one 52 meters by 52, holding the heart of the museum: the exhibition area and conference rooms.

**Gallery of the Mediterranean**

MuCEM’s permanent exhibition, the 1600 m² Gallery of the Mediterranean, uses everyday objects together with artworks to illustrate practices and beliefs representative of civilizations from the Neolithic era onwards. Four themes are covered. First, there is the birth of agriculture some 10 000 years ago...
and the emergence in early societies of belief in divinities who
governed the success or failure of crops. The second theme
is the rise of monotheistic beliefs, illustrated by the example
of Jerusalem, which became a holy site for the three main
religions of the eastern Mediterranean: Judaism, Christianity,
and Islam. The third theme relates to citizens and responsi-
bility in Mediterranean and European societies, the notion of
citizenship, from Athenian democracy to present-day human
rights. The fourth and last theme is an invitation to venture
beyond the known world, to undertake a voyage illustrated by
instruments used in maritime exploration, nautical charts, lux-
urious and exotic treasures that tell the story of man’s explo-
ration of the Mediterranean and points east.

Temporary exhibitions
This fascination with the Mediterranean was pursued further
in MuCEM’s inaugural exhibition: The Black and the Blue, A
Mediterranean Dream. The black of Francisco Goya, the blue
of Joan Miró. An exhibition that displayed, as the MuCEM
website put it: “The Enlightenment and its shadows, like two
sides of one world, a response to the very idea of civilization,
created in the 18th century.” In his Disasters of War, a set of
eighty etchings and aquatints, Goya revealed, in the words of
André Malraux, “what, in man, aspires to destroy him.” Miró’s
world, in contrast, was the sundrenched island of Majorca,
where blue was the color of his dreams. Mediterranean blue,
a symbol, an icon of man’s desire to seek within himself his
own origins. The exhibition invited visitors to travel through
time from the world of Goya (1746-1828) to the here and now,
to recount, to dream, while never forgetting history’s dark side,
for, as Walter Benjamin remarked, “there is no document of
civilization which is not at the same time a document of bar-
barism.”

Currently, one of MuCEM’s temporary exhibitions is Such a
Sweet Moment by the French photographer Raymond Dep-
dardon and his use of color from the 1950s until now. Always
present, color took on a certain dominance in Depardon’s work
from the 2000s: he moved away from reportage in a quest for
truth and happiness through rediscovery of the light and col-
ors of South America, Africa, and the United States, and a
new Mediterranean element entered his work. In the words
of French philosopher Clément Rosset, Depardon is now
seeking “the sweetness of reality.”

Another temporary exhibition, History Zero by Greek artist
Stefanos Tsivopoulos, is an installation originally commissioned
for the 55th International Art Exhibition, la Biennale di Venezia,
in 2013. History Zero casts an eye over how we value mon-
ey and its role in human relationships. Against the backdrop
of the 7th year of recession in Greece, Tsivopoulos believes that the Greek economic crisis “has to do with […] the way we perceive or approach value,” and how this perception “has been contested by different cultures, communities, and societies.” He illustrates his ideas with archival material on currencies and exchanges—from barter, shell money and trade beads, and the gift economy to the emergence of money, banking, microfinance, mobile money, and bitcoins—and a film that tells the intertwined stories of three people in Athens. Wandering the streets, an African immigrant searches for scrap metal to sell. An artist seeks inspiration in the cityscape by randomly recording street scenes with his iPad. Alone in a museum-like house, an elderly art collector afflicted by dementia spends her time folding euro banknotes into origami flowers. These acquire new value when the young immigrant happens across them in a bin, while his “treasure”—the trolley laden with scrap metal—serves to inspire the artist.

Through its permanent and temporary exhibitions, MuCEM spurs us to reflect, to be moved, to admire, and to question. Is this not the purpose of a museum seeking its place in today’s world?

LE MUCEM, FIERTÉ DE MARSEILLE

C’est un carré parfait ceint d’un voile de béton, un vaisseau noir majestueux posé entre terre et mer à l’entrée du port de Marseille. Inauguré en juin 2013, le Musée des Civilisations de l’Europe et de la Méditerranée (MuCEM) est l’un des seuls musées de province crée en France ces dernières années. Une prouesse architecturale signée de l’architecte français d’origine algérienne, Rudy Ricciotti, 62 ans. Un bâtiment étonnant que l’on vient admirer du monde entier pour la pureté de sa forme et sa résille de béton ouvragé qui rappelle les moucharabiehs arabes. Un édifice plébiscité par les Marseillais parce qu’il leur offre plus qu’une institution culturelle pluridisciplinaire, un véritable lieu de promenade qui leur permet de se réapproprier leur ville grâce à de nouvelles circulations entre le quartier historique du haut de la ville, fondée en 600 avant JC par des Grecs venus de Phocée (région de l’Anatolie en Turquie actuelle) et le port. Si la vocation du MuCEM est d’être un musée de société, s’il doit composer avec des collections hétéroclites d’art populaire (250 000 objets et centaines de milliers de documents) héritées de l’ancien Musée des Arts et Traditions Populaires à Paris, sa grande réussite est d’être parvenu dès son inauguration à présenter des expositions de très bon niveau qui nous font réfléchir. Les chefs d’œuvres d’art plastique, les trésors archéologiques et d’art contemporain côtoient les outils agricoles du 19e siècle, des vêtements traditionnels venus de toute l’Europe, une impressionnante collection de chevaux de bois ou de sifflets. Au MuCEM, l’art fait partie de la vie et nous interroge.
The Medical Faculty of Montpellier: one thousand years of medicine

by C. Régnier, France

Hard by the shores of the Mediterranean stands the oldest medical faculty in Europe. Founded in 1220, the university at Montpellier in the south of France was a crucible of learning for Jewish, Arab, and Latin-speaking physicians. It enjoyed the protection and indulgence of the counts of Toulouse, the kings of Aragon, Popes, and then the kings of France. As famous in the Middle Ages as the medical schools of Salerno, Padua, Bologna, or Paris, the Medical Faculty of Montpellier to this day enjoys an autonomy that enables it to admit students from throughout Europe. In the 1500s, when Montpellier’s economic prosperity declined, the town councilors understood that, if it was to keep its regional influence, Montpellier had to continue as a university town with the best teachers. Despite the religious conflicts that ravaged the town in the 17th century, the intellectual appeal of the Montpellier Faculty of Medicine lasted until the Revolution in 1789. Nearly half of all doctors practicing in France at the time had qualified in Montpellier. During the 18th century, the Montpellier school defended the medical-philosophical doctrine of “vitalism,” which sought to overturn ideas about human physiology, hitherto explained in terms of the laws of mechanics and chemistry alone. Paul-Joseph Barthez, a physician from Montpellier whose reputation had spread throughout Europe and who authored articles on medicine and surgery for the Encyclopedia of Diderot and d’Alembert, was a fervent advocate of vitalism, which was debated throughout Europe until the 20th century. A victim of Parisian centralism, the Montpellier Faculty of Medicine fell on hard times in the first half of the 19th century, but from 1860, with the development of viticulture, and then again in the 1960s as French settlers were repatriated after Algerian independence, the faculty expanded, a blossoming that has continued to the present day.

Standing on two low hills, the site of today’s Montpellier was, in the 2nd century BC, crossed by the Via Domitia, the first Roman road to link Gaul, Italy, and Spain, along which salt from the Mediterranean was transported to Northern Europe. Montpellier itself, however, was not founded until 985, when Count Bernard II de Melgueil granted William I of Montpellier ten hectares of arable land known variously as Mons Pessulus, “lock hill” (for its strategic position), Mons Pastellorum, “hill of pastels” (for the quality of the pigments used in dyeing cloth), or Mons Pistilarius, “hill of grocers” (because of its flourishing commerce), all of which may explain the etymology of the town’s name.1,2
The land was crossed by one of the paths along the Way of Saint James, and the village, developed around the William family château, served as a stopping place for pilgrims to Santiago de Compostela. Merchants, tradesmen, and Arab and Jewish grocers-cum-physicians came to Montpellier, and by the early 1200s the town’s population of five thousand was comparable to that of Nîmes or Narbonne. Deftly playing the game of political alliances, the William dynasty brought prosperity to Montpellier. Famed for its textile manufacturing, cosmopolitan Montpellier expanded to include two active ports (Juvenal and Lattes) and turned its hand to maritime trade with the great Mediterranean ports.1,2

Writing of Montpellier in 1165, Rabbi Benjamin of Tudela noted that: "This is a place well situated for commerce. It is about a parasang [6 kilometers] from the sea, and men come for business there from all quarters, from Edom, Ishmael, the land of Algarve, Lombardy, the dominion of Rome the Great, from all the land of Egypt, Palestine, Greece, France, Asia, and England. People of all nations are found there doing business through the medium of the Genoese and Pisans. In the city there are scholars of great eminence."3

Montpellier, crucible of Jewish, Islamic, and Christian medicine

The unofficial teaching of medicine began in Montpellier at the start of the 12th century. Epistolary exchanges between travelers passing through praise the “highly skillful and renowned physicians” who practiced there. By the late 1100s, Montpellier was already home to a small community of physicians who received students from southern Europe.4 William VIII, Lord of Montpellier, asserted the town’s medical tradition by authorizing all teachers to lecture on medicine, regardless of their background or religious denomination. The town was a melting pot of three sources of medical knowledge: Christian through the *Schola Medica Salernitana*, Arabic by virtue of Hispano-Mauresque medicine, and the Jewish medical tradition. This also ended incessant squabbling between physicians seeking to monopolize medical practice and the dissemination of learning. From its inception, the Medical Faculty of Montpellier adopted a motto that affirmed its Hippocratic liberalism: *Olim Cous nunc Monspeliensis Hippocrates,* “In times past, Hippocrates was from Cos; now he is from Montpellier.”2,5-7

In 1220, the *Universitas medicorum* of Montpellier was granted its first statutes, establishing a monopoly in the teaching and practice of medicine. Holders of the title Master Teacher of the Montpellier Faculty were accorded the right to practice medicine *hic et ubique terrarum* —here and anywhere on Earth. A distinction was drawn between Master Teachers who transmitted the medical tradition of Salerno, in Latin, and those who taught, in Arabic, the medical learning of the Arab world. Teaching consisted in reading, commenting upon, and debating—sometimes quite freely—classic Greek and Arabic medical texts. The students (laymen and monks) had a free choice of teacher and, when they felt ready, asked to sit the exams for a license to practice medicine. The first statutes did not specify the length of studies, nor how diplomas were to be awarded, but additional statutes 20 years later regulated stud-
Between the 11th and 13th centuries, eight hospitals were built outside the town of Montpellier by the William dynasty (which came to an end in 1204, for want of a male heir). Each hospital had a few dozen beds and was visited by the town’s physicians, surgeons, and apothecaries. The most famous of these hospitals was founded by the monk physician Gui de Montpellier and served Pope Innocent III as a model for the whole of Italy.2,6,9

Gilles de Corbeil, physician to King Philip II of France (reigned 1180-1223), asserted that Montpellier was the only medical school in his kingdom. Competition came from the School of Salerno (Southern Italy), which at the time was the main medical teaching center of Christendom.4,10

**Papal protection and burgeoning influence**

For commerce, as for the arts and sciences, Montpellier’s influence was at its greatest under the Kings of Aragon and under the watchful care of the 14th-century Avignon Papacy.

The University of Montpellier was created in 1289 by a papal bull (charter) issued by Pope Nicholas IV, as the faculties of law and medicine and the school of arts were merged. Whereas several schools were authorized to dispense medical knowledge, only the faculty had the right to grade the students. After three years of studies, a diploma was awarded following
An open and public debate on the writings of Hippocrates and Galen. All the teachers took part in the debate, which was held in the Saint-Firmin Church or at the basilica of Notre-Dame-des-Tables. The teachers were canons and the chancellor of the faculty was always appointed by the bishop. The students directly paid the teachers, who came to their homes to teach them, and indeed until the 14th century the Medical Faculty had no building intended for this purpose. An open and public debate on the writings of Hippocrates and Galen. All the teachers took part in the debate, which was held in the Saint-Firmin Church or at the basilica of Notre-Dame-des-Tables. The teachers were canons and the chancellor of the faculty was always appointed by the bishop. The students directly paid the teachers, who came to their homes to teach them, and indeed until the 14th century the Medical Faculty had no building intended for this purpose.4-6,8,11

The teachers could perform dissections in their homes. Contrary to a widely held view, the Church did not forbid anatomical dissections. Legal proceedings were, however, brought in cases of desecration of graves and body-snatching. Pope Boniface VIII forbade, upon pain of excommunication, the dismembering of cadavers and their boiling to strip flesh from the bones, in an attempt to counter the widespread practice of reducing bodies to expedite their transport or to dispose of mortal remains in more than one tomb.4-6,8,11

Because of this, teaching in Montpellier was freer and less dogmatic than in Paris, where the university was dependent on the court of the French kings. The university was close to the papal court, a forum for the discussions of intellectuals from throughout Christian Europe, and Montpellier physicians treated Popes and cardinals. Teachers and students alike fostered ties with the intellectual world of the Mediterranean Basin, and during the 13th century Montpellier’s influence was comparable to that of the great Italian centers of learning at Padua and Bologna. Over this period, the town’s population quadrupled to 40,000, second in France only to Paris.4,5

Town and gown: economic decline and rising prestige

The incorporation of Montpellier into France in 1350 did not alter the status of the town, which was administered by six noblemen from different guilds who were elected on the first day of March every year. Good administrators, skilled diplomats, these so-called consuls brought prosperity by providing the town with a powerful commercial fleet, by concluding alliances with the great ports of Italy and Spain, by obtaining from Pope Urban V the right to trade with “infidels,” and by supplying the courts of Europe with rare and much sought-after oriental produce. A student at Montpellier, resident in Avignon, Pope Urban V used funds from the Holy See to build the monastery of Saints-Benoît-et-Germain (which became the Faculty of Medicine in the 18th century). The College of Twelve Physicians was founded to accommodate and provide sustenance to poor students. The Kings of France regularly gave donations to the Medical Faculty of Montpellier, enabling it to balance the books and train more physicians (128 in the 14th century).4

In 1450, the Royal College of Medicine was set up in new premises near Saint Matthew’s Church and, for the first time, the Medical Faculty was housed within its own four walls. Louis XII, in 1498, enacted new rules for the organization of the Medical Faculty of Montpellier, Paris being the only faculty in the kingdom to teach medicine regularly and to award recognized diplomas. Four physician-teachers were appointed by the king and paid from the privy purse. They were held accountable for their teaching by the students, who formed a brotherhood that watched over its interests and was represented by a “procurator” who played an important role in running the faculty, both in terms of the budget and the remuneration of the teachers. In the early 16th century, the Medical Faculty decided it needed a treasurer, a beadle housed at the Royal College of Medicine, and a secretary charged with rec-
Dissection lesson at the Faculty of Medicine in Montpellier. From La Grande Chirurgie by Guy (or Gui) de Chauliac, 1363 (vellum).
© Musée Atger, Faculté de Médecine, Montpellier, France/Bridgeman Images.

Layout of the Montpellier Botanical Garden, the oldest in France, created by Pierre Richier de Belleval in 1593.
Arnaldo de Villanova (1238-1311) was physician to the Popes and to the Kings of Aragon. His eclectic legacy includes learnings from the Jewish, Arab, Greek, and Christian traditions. Considered as one of the most eminent physicians of his century, he was also an astrologist and alchemist.

Henri de Mondeville (1260-1320) taught surgery in Montpellier and pioneered detailed anatomical studies. Surgeon to Philip IV of France, at his death he left unfinished his master work *Chirurgie*, the first French treaty on surgery, which until then had been reserved for barbers.

Guy de Chauliac (1298-1368) was surgeon to the Popes in Avignon, traveled widely, and wrote *Chirurgie Magna*, which remained a classic of surgery for three centuries.

François Rabelais (≈1483-1553). Ordained as a priest in 1520, Rabelais received his doctorate in medicine in 1537, having started his career as a writer around 1530. He never stopped practicing medicine. In his five-volume work *Gargantua and Pantagruel* (1532), Rabelais mocked the Montpellier Faculty and its professors, among them his own teacher Guillaume Rondelet.

Nostradamus (1503-1566) entered the Montpellier Faculty of Medicine, but was expelled soon after on the discovery that he had worked as an apothecary (a manual trade banned by the university’s statutes). He therefore never qualified as a doctor, but nonetheless practiced medicine and pharmacy all his life. Astronomer to Queen Catherine de’ Medici, the publication of his *Prophéties* (1555) brought him fame across Europe.

Guillaume Rondelet (1507-1566) was a professor at the Montpellier Faculty of Medicine and the teacher of Rabelais, who used him as a model for his character Rondibilis in the third volume of *Gargantua and Pantagruel*. He organized the first courses in botany in France and was the Chancellor of the University.

Théophraste Renaudot (1586-1653) was awarded his doctorate in medicine in 1606, and much later (1631) founded *La Gazette de France*, one of the country’s first newspapers. In Paris, he organized a *bureau d’adresses* where job offers and applicants were brought together in an attempt to remedy poverty and homelessness. He also set up a dispensary where the indigent could seek free medical consultations.

Raymond VieuSSens (1641-1715) was physician to Louis XIV and to his first cousin the Duchess of Montpensier. He was a member of the French Academy of Sciences and of the Royal Society of London. He gave his name to numerous anatomical structures and was one of the pioneers of the study of heart valve diseases.

François Gigot de la Peyronie (1678-1747), first-surgeon to Louis XV, was instrumental in the separation of the guild of surgeons from the guild of barbers. He initiated the modern teaching of surgery, founded the French Royal Academy of Surgery, and wrote its statutes. He described a disorder involving induration of the corpora cavernosa of the penis, which is now known as Peyronie’s disease.

Jean Astruc (1684-1766), professor of medicine at Montpellier, was consulting physician to Louis XV. A member of the Academy of Medicine, erudite, polyglot, he invented bibliographic research and wrote the first major treatise on syphilis and venereal diseases.

François Boissier de Sauvages (1706-1767) was a botanist and for 18 years conservator of Montpellier’s botanical garden. He drew up a renowned nosology that for many years was authoritative.

Paul Joseph Barthez (1734-1806), a leading contributor to the *Encyclopedia* of Diderot and d’Alembert, was honorary professor at the Montpellier faculty, senior member of the Council of State, consultant physician to the king, physician to Napoleon Bonaparte, and member of several European learned societies. He originated the famous vitalist doctrine of the Montpellier School.
ording diplomas and organizing examinations. Even though the royal power ceaselessly increased its influence over the Medical Faculty, the Bishop of Montpellier retained, until the Revolution, the right to inspect the administration of the faculty.4,6

The Montpellier consuls continually promoted the development of the university and of the Medical Faculty to sustain the town’s intellectual appeal. The departure of the Popes from Avignon (in 1419) triggered a decline in Montpellier’s prosperity, exacerbated by increased commerce in the Rhône Valley and the silting up of the ports of Lattes and Aigues-Mortes, the town’s main outlets to the sea. This benefited Marseille, which was attached to the French crown in 1481, and which had become an active, rival port. During the 15th century, Montpellier’s population dropped to 15 000.1,2

The Reformation reached Montpellier in the 16th century and swayed its intellectuals, wealthy merchants, and artisans, but violent clashes between Protestants and Catholics during the French Wars of Religion drove the town to ruin. Yet the Medical Faculty of Montpellier, famed as it was for its prestigious professoriat, was still able to attract students from all over Europe. In the mid-1500s, teachers were given the right to elect their chancellor and the main disciplines (surgery, pharmacy, botany, and anatomy) were defined. Thereafter, teachers were recruited following a competitive exam at which candidates competed before a board of examiners in answering randomly chosen questions on medicine.

The 16th century saw the building in Montpellier of the first anatomy amphitheater in France and the creation of chairs of anatomy and of surgery. From then onwards, the reputation of the Montpellier anatomists and surgeons steadily grew and new anatomical descriptions abounded: the caro quadrata sylvi (muscle) and os sylvi (lenticular process of incus) of Jacobus Sylvius, (Gaspard) Bauhin’s (ileocecral) valve, the reservoir of (Jean) Pecquet or receptaculum chyli, and Raymond Vieussens, who gave his name to a centrum (centrum semiovale), a brain ventricle (cavity of septum pel-lucidum), foramina (openings of smallest cardiac veins), a valve (superior medullary velum), an isthmus (limbus of fossa ovalis), an ansa (subclavian loop), ganglia (celiac ganglia), and veins (innominate cardiac veins).2,4,5

In 1593, Henri IV encouraged the creation of France’s oldest botanical garden, the Jardin des Plantes de Montpellier, by Pierre Richer de Belleval, holder of the newly created Chair of botany at Montpellier. The gardens are still one of the finest examples of Montpellier’s cultural heritage.5,6,1

The teaching of Arab medical authors dwindled from the 15th century and by 1646 had disappeared altogether. Likewise, the teaching of Greek medicine was progressively removed from the program of studies during the 17th century. In 1715, the number of teachers increased from four to eight, and thereafter bore the title professor and occupied chairs. New disciplines emerged, such as chemistry, the chair of which was created in 1673.4,6

The doctrine of vitalism in Montpellier

Having rid itself of ancient theories, 18th-century medicine incorporated chemistry and physics in an attempt to explain the phenomena of life. This was a time characterized by lively debates and heated controversies between medical movements, schools of thought, and the defenders of medical and philosophical doctrines. This intense intellectual activity heralded medicine’s entry into the modern era, with the emergence of new subjects like biology, physiology, anatomical pathology, and histology.

In France, the doctrine of vitalism was born in Montpellier, enunciated by Théophile de Bordeu and Paul-Joseph Barthez, professors famed throughout 18th-century Europe. This doctrine asserted that the phenomena of life were not subject solely to the laws of physics and chemistry, but also to a “vital force.” Collaborator at the Journal des Savants, Barthez was the author of over 2000 articles on medicine and surgery for the Encyclopedia of Diderot and d’Alembert. Barthez

François Gigot de Lapeyronie, also spelled la Peyronie (1678-1747), first-surgeon to King Louis XV. Painting by Hyacinthe Rigaud (1659-1743), at the Paris Museum of History of Medicine. © Bridgeman Images.
Museum of Anatomy (Conservatoire d’Anatomie) of the Faculty of Medicine of Montpellier, and its emblematic digging écorché created in 1858 by Alphonse Lami (1822-1867).

© Pascal Parrot.
held that man comprised three elements: organized matter or body, the soul, and the vital (or life) force. He believed that medicine and the study of life should shed the century-old straitjacket imposed by the “mechanistic” theory of Descartes. With the development of the microscope and observations of living tissue, anatomists were certain that the phenomena of life could no longer be explained just by the laws of mechanics. Barthez wondered whether the vital principle had an independent existence or instead infused life into the human body.6,13-16

In a talk at the Medical Faculty of Montpellier in 1792, the chemist Jean Antoine Chaptal characterized the “vitalist spirit” by the view that he who studies bodily functions alone will never be a physician, because while he thinks he knows man, in fact all he knows is the outer shell, the carcass. Such an approach, Chaptal argued, would overlook the fine connections between man and his surroundings, reciprocal action and reaction with other bodies, the great system of movement that fashions from all living things the organs of a larger whole.15,16

The vitalist theory of the Montpellier school created a stir throughout Europe. Fiercely contested in Paris, it was seen as far removed from the anatomical and clinical studies that Parisian physicians deemed essential to pathophysiological understanding. The physicians of the Medical Faculty of Paris had their own “organicist” school of thought, based on the anatomical and clinical method.

In the late 18th century, Xavier Bichat applied the vitalist principle to his definition of life as an ensemble of functions that oppose death. This vitalist theory was combated by Jean-Baptiste de Lamarck, the originator of the theory of transformism, or the transmutation of species, and in the 19th century by Claude Bernard, who deemed it incompatible with the principles of “experimental medicine”: “Vitalism runs counter to the scientific spirit (…) At the heart of vitalist doctrines there is an irreparable error, which is to lend real existence (…) to something immaterial, something which in reality is just a notion of the spirit.” The vitalist theory debate between physicians raged on unabated for years.6,13-16

Revolutionary upheaval

The French Revolution passed almost unnoticed in Montpellier, which was spared bloody riots and mass executions. The consuls who administered the town gave way to an elected town council directed by a mayor. The “enlightened” bour-
geoisie infiltrated the administrative machinery and took control. Somewhat predisposed to moderate revolutionary ideas, the bourgeoisie lived through the Revolution without mishap. The populations of the town and the surrounding countryside, however, suffered greatly from food shortages, military requisitions, and, above all, a cholera epidemic, which killed one-tenth of them (2500 people).1,2,17

The National Convention in 1793 promulgated the dissolution of “antiquated” universities and the closure of “medieval” schools. Already closed were the corporations, the academies, and the learned societies, charged with having “sequestered” learning. In Montpellier, far from the prying eyes of the political powers in Paris, the Medical Faculty unobtrusively continued throughout the Revolution to accept and train students and to award diplomas.

A decree the following year ordered the reopening of the School of Health in Montpellier (and also those of Paris and Strasbourg) and stipulated the number of students admitted to each: 300 in Paris, 150 in Montpellier, and 100 in Strasbourg. Typical of the Paris-centric mentality of the elected members of the National Convention, the law arbitrarily reduced student numbers in Montpellier and imposed Paris as the leading Medical Faculty in France. The Paris School also benefited from institutions such as the Collège de France and the Museum of Natural History, which facilitated research. This harmonization of teaching and courses at the three medical schools ended the Montpellier Faculty of Medicine’s centuries-old tradition of independence.14,17

Montpellier’s physicians nonetheless remained influential in France and elsewhere in Europe. An early 19th-century survey by the Ministry of the Interior indicated that of 2398 physicians practicing in France, 1101 had trained in Montpellier, 226 in Toulouse, 195 in Caen, and 72 in Paris. It should be borne in mind, however, that many physicians, having started their studies in Paris, completed them in Montpellier, where the enrolment fees were lower.1,14,17

In 1795, the Montpellier Medical School moved into its current premises, the Saint Benoit monastery adjoining the Saint-Pierre Cathedral. Jean-Antoine Chaptal had the anatomy lecture hall built and saw to the transfer from Paris of a collection of wax anatomical models by the 18th-century Tuscan artist Felice Fontana, for display in the newly created museum of anatomy.

Chaptal appointed Gabriel Prunelle inspector of libraries and of book depositories and charged him with the creation of the Medical Faculty’s library, which currently holds 300 incunabula (books printed before 1501), 100 000 volumes printed before 1800, and all the theses of the medical faculties of Montpellier and Paris since the 17th century. Known to all medical students in France, this catalog of riches was the fruit of Gabriel Prunelle’s vigorous policy of acquisition of works and of library collections throughout Europe.14,17

In the early 1800s, the Medical Schools once more became Faculties of Medicine, the doctorate was restored, and the wearing of professorial gowns was rehabilitated, in a move towards the organization of an imperial university, which reintroduced competitive exams for the recruitment of professors.

Epilogue

In the mid–19th-century, the town of Montpellier suffered demographic, economic, and even academic decline. The Faculty of Medicine lost its shine and was training only 700 students a year. But the town’s fortunes turned once more. The spectacular growth of the railroad network expedited the transportation of large volumes of wine and Languedoc and Montpellier developed winegrowing, leading to a flourishing wine trade.1 The number of medical students rose to 1500 by the early 1900s and to nearly 3000 on the eve of World War 2.4

Boosted by the return of French settlers repatriated after Algerian independence in 1962, Montpellier, as the capital of Languedoc, regained its regional influence in politics, culture, economics, and learning. Most of the university’s faculties were rebuilt or refurbished and the number of students rose to 50 000 by 1990.4 By mid-2014 the University of Montpellier I, the heir to the School of Medicine founded in 1220, counted over 22 000 medical students.

Anatomical wax head by Felice Fontana (1730-185), at the Museum of Anatomy of the Faculty of Medicine of Montpellier. © Pascal Parrot.
LA FACULTÉ DE MÉDECINE DE MONTPELLIER : MILLE ANS DE MÉDECINE


References
Sign up for e-mail notification of the contents of forthcoming issues of Medicographia
International Advisory Committee
"Chance favors only the prepared mind"

Pasteur

The vulnerable phase of heart failure: a window of opportunity