Heart failure today: a paradigm shift
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Heart rate is an easily assessable biologic parameter. It is a risk factor for future death and cardiovascular events in epidemiologic studies in patients with hypertension as well as in those with established vascular disease.1 Heart rate, together with stroke volume, controls cardiac output and is thus an important regulator of exercise performance. Resting heart rate thus determines oxygen consumption both in the body overall and also in the myocardium. Together with systolic blood pressure, heart rate regulates myocardial oxygen consumption, which can induce myocardial ischemia if the heart rate becomes excessively high.

Resting heart rate also seems to be adjusted by a biologic clock, and the total number of heart beats per minute in mammals seems to be related to body size.2 Elevated heart rate is associated with reduced myocardial function in experimental settings, and there are various pathophysiologic mechanisms for the development of cardiovascular and myocardial dysfunction caused by tachycardia.3 When myocardial function is diminished, as in heart failure with reduced systolic function, myocardium is energetically starved and elevated heart rate has added negative consequences, including progressive mechanical dyssynchrony and reduced inotropy.4 In heart failure with impaired left ventricular systolic function, heart rate becomes even more important, and to some extent crucial. Many years ago, we realized that elevated heart rate might be a major determinant of prognosis in patients with idiopathic dilated cardiomyopathy (IDCM). The hypothesis was based on clinical observations together with animal experimental findings. Drs Waagstein and Hjalmarson tested these thoughts in practice and found that some patients with IDCM seemed to improve when heart rate was reduced with a β-blocker.5

We expanded on this observation. With our approach, we initiated a β-blocker (first practolol then metoprolol) at a very low dose. We slowly increased the dose, every second or third day in hospitalized patients and every week in ambulatory patients, and carefully monitored dyspnea together with heart rate and blood pressure.

Doses of β-blocker were doubled until either heart rate was reduced to below 70 bpm or symptomatic hypotension occurred. Thus, heart rate was the most important biologic marker we used for dosing. In our reports on the first 28 patients, we speculated on the mechanisms for the improvement of myocardial function.6 At the time, we thought that catecholamine-induced myocardial toxicity was driving myocardial failure and that heart rate was a reflection of this drive.

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**Further research**

Over the next 20 years, several randomized studies followed, and the use of β-blockade became very well documented with marked beneficial effects on mortality and morbidity. With the help of large databases, retrospective analyses were published in order to tease out the importance of heart rate. Wikstrand et al presented an analysis from MERIT-HF (MEtoprolol MR/XL Randomized Intervention Trial in congestive Heart Failure), where they compared patients who had tolerated ≤100 mg (mean 76 mg) of metoprolol succinate versus those who had tolerated >100 mg (mean 192 mg). They found that baseline heart rate as well as changes in heart rate were of significant importance for further survival. However, they also found that the benefit of bisoprolol on survival was not influenced by the level of baseline heart rate or by the extent of heart rate reduction. They then concluded that the data clearly indicate that heart rate reduction is not the only mechanism responsible for β-blocker-induced benefit in heart failure.

These retrospective analyses support the hypothesis that heart rate and changes in heart rate are key factors in the management of patients on β-blockers. However, β-blockers have several effects on the cardiovascular system, and the importance of these effects is unclear. Further support for the relationship between changes in heart rate and improved myocardial function and outcome was presented by Flannery et al in a meta-regression analysis of β-blocker trials. Thirty-five trials, which included 22,926 patients with a mean follow-up of 9.6 months, were analyzed to determine all-cause mortality, left ventricular ejection fraction, and heart rate. There was a close relation between all-cause annualized mortality and heart rate (adjusted r=0.51, P=0.004), and a strong correlation between change in heart rate and change in left ventricular ejection fraction (adjusted r=0.48, P≤0.001) was also observed. When only trials with >100 patients were included, an even tighter correlation was seen (adjusted r=0.60, P=0.0004).

In a meta-analysis of 23 trials of β-blockers in heart failure where mortality was reported, which included 19,209 patients, McAlister et al presented data on heart rate versus other variables for outcome. In a meta-regression analysis, the degree of heart rate reduction was the only remaining significant variable of prognostic importance. For every 5 bpm reduction, the risk of death decreased by 18%. They were also able to analyze low versus high dose in 19 trials, and this variable was not of prognostic importance.

These data are consistent with the findings in the BEAUTIFUL (morBidity-mortality EvAlUaTion of the iβ inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) study, where the sinus node inhibitor ivabradine was used. BEAUTIFUL included patients aged 55 years or older with coronary artery disease and left-ventricular ejection fraction of less than 40%. The patients were in sinus rhythm and had a resting heart rate of 60 bpm or greater. Analyses of baseline heart rate as a continuous variable showed that, for every increase of 5 bpm, there is an 8% increase in cardiovascular death (P=0.0005), a 16% increase in admission to hospital for heart failure (P<0.0001), a 7% increase in admission to hospital for fatal and nonfatal myocardial infarction (P=0.052), and an 8% increase in coronary revascularization (P=0.034).

In a follow-up publication from SHIFT (Systolic Heart failure treatment with the iβ inhibitor ivabradine Trial), heart rate at baseline was analyzed in relation to various outcomes. SHIFT included patients with chronic heart failure and an ejection fraction ≤35% who were in sinus rhythm and on recommended therapy. When the placebo group was divided by heart-rate quintiles at baseline, the incidence of the primary composite end point and its components was greatest in patients with high heart rates. Patients in the group with the highest heart rate at baseline (≥87 bpm) had more than twice the risk for the primary composite end point than those in the lowest heart rate group (70 to <72 bpm; hazard ratio, 2.34; 95% confidence interval, 1.84 to 2.98; P<0.0001). In the placebo group, analysis with heart rate as a continuous variable showed that for every beat increase in heart rate, the risk of a primary composite end point event increased by 3% (P<0.0001).

**Mechanisms**

There are several potential mechanisms for improved myocardial function with reduction in heart rate. In the recent paper from SHIFT, Böhm et al suggested that heart rate is directly associated with atherogenesis in disease models. Failing human myocardium has a negative force-frequency associ-
and is energetically starved. They also concluded that previous evidence suggests that heart rate reduction can improve contractility and energy supply, while reducing energy expenditure. My personal view is that in myocardium where rate dependency is present, rate-limiting ATP synthesis is also present. When there is more time, ATP synthesis is restored. However, previous studies have not been able to separate the effects of pure heart rate changes from the effects of β-adrenergic signaling modifications.

**Summary**

Heart rate is an important and easily accessible physiologic variable with prognostic and clinical importance. In chronic heart failure, changes in heart rate are even more important as myocardial performance is compromised. Control of heart rate with a β-blocker is important. Further control of heart rate beyond and above that achieved with a β-blocker provides added value. The potential of ivabradine in this context is therefore interesting and welcome.

**References**


**Keywords:** heart rate; heart failure; management
La fréquence cardiaque est un paramètre biologique facilement mesurable. Elle constitue un facteur de risque de mortalité et d’événements cardio-vasculaires dans les études épidémiologiques effectuées chez des patients hypertendus, ou atteints de maladies vasculaires établies. La fréquence cardiaque, avec le débit systolique, contrôle le débit cardiaque, et constitue par conséquent un régulateur important des performances à l’effort. La fréquence cardiaque au repos détermine la consommation d’oxygène dans l’organisme en général ainsi que dans le myocarde. Avec la pression artérielle systolique, la fréquence cardiaque régit la consommation myocardique d’oxygène, ce qui peut induire une ischémie myocardique si la fréquence cardiaque devient excessivement élevée.

La fréquence cardiaque au repos semble également s’ajuster à l’horloge biologique, et le nombre total de battements cardiaques par minute chez les mammifères semble être lié à la taille du corps. L’augmentation de la fréquence cardiaque est associée à une réduction de la fonction myocardique dans des conditions expérimentales, et un certain nombre de mécanismes physiopathologiques interviennent dans le développement d’un dysfonctionnement cardio-vasculaire et myocardique si la fréquence cardiaque devient excessivement élevée.

Lorsque la fonction myocardique diminue, comme dans l’insuffisance cardiaque avec réduction de la fonction systolique, le myocarde a besoin d’importantes quantités d’énergie et l’augmentation de la fréquence cardiaque a des conséquences négatives supplémentaires, notamment une dysynchronie mécanique progressive et une réduction de l’inotropisme. Dans l’insuffisance cardiaque avec altération de la fonction systolique ventriculaire gauche, la fréquence cardiaque devient encore plus importante, et dans une certaine mesure cruciale. Il y a de nombreuses années, nous nous sommes rendu compte que l’augmentation de la fréquence cardiaque pouvait constituer un déterminant majeur du pronostic chez les patients atteints de cardiomyopathie idiopathique dilatée (CMID). L’hypothèse reposait sur des observations cliniques ainsi que sur des expérimentations chez l’animal. Les docteurs Waagstein et Hjalmarson ont testé ces suppositions et ont constaté que l’état de santé de certains patients atteints de CMID semblait s’améliorer lorsque la fréquence cardiaque était réduite à l’aide d’un bêtabloquant.

Nous avons prolongé cette observation. Avec notre approche, nous avons commencé un traitement par un bêtabloquant (d’abord le practolol puis le métoprolol) à une dose très faible. Nous avons lentement augmenté la dose, tous les deux ou trois jours chez des patients hospitalisés, et toutes les semaines chez des pa-
tients ambulatoires, et nous avons étroitement surveillé la dyspnée ainsi que la fréquence cardiaque et la pression artérielle. Les posologies du bêtabloquant ont été doublées jusqu’à ce que la fréquence cardiaque soit réduite au-dessous de 70 bpm ou qu’une hypotension symptomatique survienne. La fréquence cardiaque a été le marqueur biologique le plus important que nous avons utilisé pour la posologie. Dans nos comptes rendus sur les 28 premiers patients, nous avons émis des hypothèses sur certains mécanismes entraînant l’amélioration de la fonction myocardique. À cette époque, nous pensions que la toxicité myocardique induite par les catécholamines était le moteur de l’insuffisance myocardique, et que la fréquence cardiaque était le reflet de son action.

Recherches complémentaires

Au cours des 20 années suivantes, plusieurs études randomisées ont été réalisées, et l’utilisation des bêtabloquants a fait l’objet d’une abondante documentation concernant ses effets bénéfiques marqués sur la mortalité et la morbidité. Avec l’aide de larges bases de données, des analyses rétrospectives ont été publiées afin d’explorer l’importance de la fréquence cardiaque. Pikstrand et coll. ont présenté une analyse de l’étude MERIT-HF (MEtoprolol MR/XL Randomized Intervention Trial in Congestive Heart Failure, Étude interventionnelle randomisée avec le métoprolol à libération modifiée/prolongée dans l’insuffisance cardiaque congestive), où ils comparaient les patients ayant toléré ≤ 100 mg (en moyenne 76 mg) de succinate de métoprolol par rapport à ceux ayant toléré > 100 mg (en moyenne 192 mg). La fréquence cardiaque obtenue a été la même dans les deux groupes, 67 bpm, et même si la mortalité a été supérieure dans le groupe de la dose faible, la réduction de la mortalité a été identique quelle que soit la dose de bêtabloquant utilisée. Les auteurs ont conclu que les résultats confirmaient l’idée d’un schéma individualisé d’ajustement posologique, guidé par la tolérance des patients et la réponse au niveau de la fréquence cardiaque.

Lechat et coll. ont étudié la fréquence cardiaque initiale et les changements de la fréquence cardiaque au cours de l’étude CIBIS II (Cardiac Insufficiency Bisoprolol Study II, Étude sur le bisoprolol dans l’insuffisance cardiaque II). Ils ont observé que la fréquence cardiaque initiale ainsi que les changements de la fréquence cardiaque revêtaient une importance significative pour la survie ultérieure. Cependant, ils ont également constaté que le bénéfice du bisoprolol sur la survie n’était pas influencé par le niveau de la fréquence cardiaque initiale ou par l’amplitude de la réduction de la fréquence cardiaque. Ils ont par conséquent conclu que les données indiquaient clairement que la réduction de la fréquence cardiaque n’était pas le seul mécanisme responsable du bénéfice induit par les bêtabloquants dans l’insuffisance cardiaque.

Ces analyses rétrospectives confirment l’hypothèse selon laquelle la fréquence cardiaque et ses changements sont des facteurs essentiels dans la prise en charge des patients sous bêtabloquants. Cependant, les bêtabloquants ont plusieurs effets sur le système cardio-vasculaire, et l’importance de ces effets n’a pas été clairement établie. Une confirmation du lien de cause à effet entre les changements de la fréquence cardiaque et l’amélioration de la fonction et de l’évolution du myocarde a été présentée par Flannery et coll. dans une analyse de méta-régression des études sur les bêtabloquants. Trente-cinq études, qui ont inclus 22 926 patients avec un suivi moyen de 9,6 mois, ont été analysées afin de déterminer la mortalité de toute cause, la fraction d’éjection ventriculaire gauche et la fréquence cardiaque.

Il a été observé une relation étroite entre le taux de mortalité de toute cause annuaire et la fréquence cardiaque (r ajusté = 0,51 ; p = 0,004), et une forte corrélation entre le changement de la fréquence cardiaque et le changement de la fraction d’éjection ventriculaire gauche (r ajusté = 0,48 ; p ≤ 0,001) a également été observée. Lorsque seules les études comprenant plus de 100 patients ont été incluses, une corrélation encore plus étroite a été constatée (r ajusté = 0,60 ; p = 0,0004).

Dans une méta-analyse de 23 études ayant inclus 19 209 patients menées sur les bêtabloquants dans l’insuffisance cardiaque, dans lesquelles la mortalité a été rapportée, McAlister et coll. ont présenté des données sur la fréquence cardiaque par rapport à d’autres variables sur les résultats cliniques. Dans une analyse de méta-régression, le degré de réduction de la fréquence cardiaque a été le seul paramètre significatif restant qui présentait une importance pronostique. Pour chaque réduction de 5 bpm, le risque de mortalité a diminué de 18 %. Les auteurs ont également été en mesure d’analyser les doses faibles par rapport aux doses élevées dans 19 études, mais cette variable n’a pas montré d’importance pronostique.

Ces données concordent avec les résultats de l’étude BEAUTIFUL (morBidity-mortality EvAluATion of the ß inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction, Évaluation de la morbidité et de la mortalité avec l’ivabradine, un inhibiteur du courant lent, chez des patients atteints de coronaropathie et de dysfonctionnement ventriculaire gauche), dans laquelle un inhibiteur du nœud sinusal, l’ivabradine, a été utilisé. L’étude BEAUTIFUL a inclus des patients âgés de 55 ans et plus atteints de coronaropathie dont la fraction d’éjection ventriculaire gauche était inférieure à 40 %. Les patients présentaient un rythme sinusal et une fréquence cardiaque au repos de 60 bpm ou plus. Les analyses de la fréquence cardiaque initiale considérée comme variable continue ont montré que, pour chaque augmentation de 5 bpm, la mortalité cardio-vasculaire augmentait de 8 % (p = 0,0005), les hospitalisations pour insuffisance cardiaque de 16 % (p < 0,0001), les hospitalisations pour infarctus du myocarde fatal et non fatal de 7 % (p = 0,052), et les revascularisations coronaires de 8 % (p = 0,034).
Dans une publication de suivi de l’étude SHIFT (Systolic Heart failure treatment with the I, inhibitor ivabradine Trial, Étude sur le traitement de l’insuffisance cardiaque systolique par l’iva-bradine, un inhibiteur du courant If), la fréquence cardiaque initiale a été analysée en relation avec différents critères d’évaluation. L’étude SHIFT a inclus des patients atteints d’insuffisance cardiaque chronique dont la fraction d’éjection était ≤ 35 %, présentant un rythme sinusal et recevant le traitement recommandé. Lorsque le groupe placebo a été divisé par quintiles de fréquence cardiaque à l’inclusion, l’incidence du critère composite principal et de ses différents composants a été supérieure chez les patients présentant les fréquences cardiaques élevées. Les patients du groupe présentant la fréquence cardiaque maximale à l’inclusion (≥ 87 bpm) ont plus que doublé le risque du critère composite principal par rapport à ceux appartenant au groupe de la fréquence cardiaque la plus faible (70 à < 72 bpm ; risque relatif : 2,34 ; intervalle de confiance 95 % : 1,84 à 2,98 ; p < 0,0001). Dans le groupe placebo, l’analyse utilisant la fréquence cardiaque comme variable continue a montré que pour chaque augmentation d’un battement de la fréquence cardiaque, le risque d’un événement correspondant au critère composite principal augmentait de 3 % (p < 0,0001).

Mécanismes
Plusieurs mécanismes potentiels peuvent être évoqués pour l’amélioration de la fonction myocardique par la réduction de la fréquence cardiaque. Dans le récent article de l’étude SHIFT, Böhm et coll. ont suggéré que la fréquence cardiaque était directement associée à l’athérogenèse dans des modèles pathologiques. Le myocarde humain déficient montre une association négative entre force et fréquence et présente d’importants besoins énergétiques. Les auteurs ont également conclu que des preuves antérieures suggéraient qu’une réduction de la fréquence cardiaque pouvait améliorer la contractilité et l’apport énergétique, tout en réduisant les dépenses énergétiques.

Mon avis personnel est que dans le myocarde présentant une dépendance par rapport à la fréquence, une synthèse d’ATP limitant la fréquence est également présente. Avec plus de temps, la synthèse d’ATP est rétablie. Cependant, des études antérieures n’ont pas été en mesure de séparer les effets des seuls changements de la fréquence cardiaque des effets des modifications de la signalisation bêta-adrénnergique.

Résumé
La fréquence cardiaque est un paramètre physiologique important et facilement accessible présentant une importance pronostique et clinique. Dans l’insuffisance cardiaque chronique, les changements de la fréquence cardiaque sont même plus importants, car les performances myocardiques sont altérées. Le contrôle de la fréquence cardiaque par un bétabloquant est important. Un contrôle supplémentaire de la fréquence cardiaque au-delà de celle obtenue par un bétabloquant apporte une valeur supplémentaire. Les caractéristiques de l’ivabradine dans ce contexte sont par conséquent intéressantes et bienvenues.
Heart failure constitutes an important medical, social, and economic problem. Although reliable estimates are lacking in many countries, the prevalence of heart failure is estimated as 2%-3% of the adult population and increases with age. Over 26 million people suffer from heart failure around the world and over 3.5 million people are newly diagnosed with heart failure every year in Europe alone. The long-term prognosis associated with heart failure is worse than that associated with the majority of cancers, with 50% mortality after 4 years. Patients suffer disabling symptoms that often become refractory to treatment and need hospitalization, having the greatest negative impact on quality of life compared with other chronic conditions. The cost of medical care is measured in billions of dollars. The prevalence of heart failure progressively increased from the early 1950s onwards for 30 years, eventually reaching a plateau. However, it is likely we will observe a new increase in the future mainly because of the aging of the population and because of the trend showing an increasing prevalence of major heart risk factors, including obesity and diabetes. The challenge of preventing a heart failure pandemic in the future is important for all countries, but especially those with economies in transition, where traditional healthy lifestyles are quickly changing. The only way of avoiding this new pandemic is through prevention, which is the collective responsibility of everyone: physicians, education and health authorities, and patients.

Although not a heart disease itself, heart failure (HF) is a heart condition with a high social, sanitary, and economic impact. Reliable estimates of HF are lacking in many countries because of the absence of reliable surveillance programs to track the incidence, prevalence, outcomes, as well as the key causes of HF. According to estimates from the European Heart Failure Association, 26 million people have HF worldwide and 3.6 million people are newly diagnosed with HF every year in Europe alone. Similar figures are reported by the National Institute of Health in the United States, and an absolute increase is expected in future years.

The long-term prognosis associated with HF is poor. Half of all patients diagnosed with HF die within 4 years, and the 5-year survival rate is lower than that associated with myocardial infarction and the majority of major malignancies. HF has the greatest negative impact on quality of life compared with other major chronic disease, such as diabetes, arthritis, and hypertension. Patients with HF suffer disabling
symptoms, especially after their first hospitalization, the most common of which are fatigue and dyspnea, while in terms of disability, the end stage of the disease is comparable to that of terminal cancer.

The economic cost of HF is estimated in billions of dollars per year, the need for repeated hospitalization being the most powerful contributing factor to direct costs associated with the disease. The longer life expectancy of the population, better treatment of heart diseases, and increase in risk factors for ischemic heart disease, particularly in countries with economies in transition, account for a growing incidence and prevalence of HF around the world. The only way to decrease the oncoming pandemic is by reducing the risk factors for cardiovascular diseases and HF through treatment, education of the population, and legislation for a healthier lifestyle. This is a responsibility that concerns not only physicians, but also teachers, health care providers, and patients.

The difficulties of defining and classifying heart failure
HF is a complex syndrome, clinically characterized by signs and symptoms secondary to abnormal cardiac function. It includes patients with impaired (systolic HF) or preserved systolic left ventricular function (diastolic HF). Left ventricular function is below normal limits in a significant number of otherwise normal individuals (asymptomatic left ventricular dysfunction), and the process itself may be considered as a progressive disorder ranging from risk factors to heart disease, asymptomatic impaired ventricular function, symptomatic HF, and finally refractory or advanced HF (Figure 1)

Incidence and prevalence
Incidence (number of new cases per year) and prevalence (proportion of the general population with HF) figures reported in the medical literature vary widely, mainly because different sets of diagnostic criteria have been used. Contemporary studies estimate the overall prevalence of HF in the US population to be about 2%-3%. Although significant differences have been noted between studies in different countries (Figure 2), in general, HF prevalence in Western European populations is estimated to range from 0.4% to 2%. There is no agreement over a simple definition of HF for epidemiologic studies.

Systolic versus diastolic heart failure
Asymptomatic diastolic left ventricular dysfunction, manifested by severe left ventricular hypertrophy and/or abnormal echocardiographic parameters, is frequently found in patients with hypertension and other clinical conditions, such as ischemic heart disease. Although the majority of these patients never present signs or symptoms of HF, there is a lack of reliable, universal tools for diagnosis in epidemiologic studies.

Effective therapies to prevent HF and improve outcomes

Figure 1. The progression of heart failure.
Heart failure is a progressive disorder, ranging from normal ventricular function in the absence of heart disease in the presence of risk factors to severe ventricular dysfunction with symptoms refractory to treatment. An elusive clinical diagnosis and the lack of reliable, universal tools for diagnosis in epidemiologic studies explain discrepancies in heart failure prevalence and incidence between different studies. Abbreviations: HF, heart failure; LV, left ventricular; NYHA, New York Heart Association (classification).
clear relationship between diastolic functional abnormalities and long-term hospital admission for HF and, in general, worse outcomes compared with patients with normal diastolic function. If the diagnosis of HF with depressed systolic ventricular function is considered elusive, then the correct diagnosis of diastolic HF is a real clinical challenge. Both European and American cardiology associations offer recommendations for the correct diagnosis of diastolic HF that go well beyond the tandem of HF symptoms in the presence of normal left ventricular ejection fraction (LVEF). The relative complexity of the diagnosis may be a problem in everyday clinical practice, but it is a real challenge to ascertain the type of HF, either systolic or diastolic, when conducting epidemiological studies. Accordingly, the information relative to this type of HF is found mainly in registries rather than in prospective, population-based epidemiologic studies. With all the aforementioned limitations, the incidence and prevalence of diastolic HF is probably about the same as HF with depressed left ventricular contractility.

**Incidence**

In the Olmsted County study (Minn, USA), 137 patients with new HF presenting in 1991 had a recent echocardiogram assessing LVEF, which showed that 43% of them had an LVEF above 50%, qualifying as HF with preserved systolic function. However, in another population-based study, Cowie et al in London performed an echocardiogram in 93% of all new, local cases of HF and only 16% presented a normal LVEF, while there was a mild to moderate reduction in LVEF in 68%, and a severe reduction in LVEF in 16%. Again there was the problem of defining normal limits of systolic function parameters.

**Prevalence**

In cross-sectional population studies, the proportion of patients with preserved systolic function HF range from 40% to 70%, with an average of about 50% (Figure 3). In the Euro-
Heart Failure Survey I, 51% of men, but only 28% of women, had an LVEF <40%. In contrast, in the EuroHeart Failure Survey II in patients hospitalized with acute HF, preserved LVEF ≥45% was present in 34.3% of the whole study population (42.8% in de novo acute HF vs 29.6% in acutely decompensated chronic HF patients). In addition, patients with diastolic HF are older and present more comorbidities than patients with left ventricular systolic dysfunction, and treating patients with diastolic HF remains a diagnostic and therapeutic challenge in clinical practice.

Asymptomatic left ventricular dysfunction
A surprisingly large number of otherwise normal individuals in the general population present systolic function indexes well below the normal limits, the majority without signs or symptoms of HF. In the Glasgow study, part of the MONICA (MONItoring CArdiovascular disease) project, 2.9% of 1467 normal individuals without previously known heart disease, aged 25 to 75 years, presented a LVEF <30%, of whom about 50% were completely asymptomatic (Figure 4).

In the Rotterdam study, which included 5540 participants aged over 55 years, the prevalence of HF was 3.9%, and 3.7% presented a left ventricular fractional shortening <25%, a measure of systolic left ventricular dysfunction. Curiously, only 20% of patients with systolic dysfunction presented clinical HF, and 60% of patients with left ventricular systolic dysfunction had no symptoms or signs of HF at all.

A true epidemic
HF statistics all over the world are overwhelming (Table I). It is estimated that 26 million people have HF worldwide, up to 6 million American and as many Europeans suffer from HF, and 1 million people are newly diagnosed with HF every year in the USA and the European Union alone. These figures imply that the risk of having HF in a lifetime is 1 in 5.

Past, present, and future prospects
The worldwide prevalence of HF has been increasing during the last few decades, something that could be attributed to several factors: an increase in the incidence of cardiovascular diseases; an aging population; better and more effective treatment of heart disease in general and acute coronary syndromes in particular, leading to a reduction in short-term mortality and HF occurring over a longer time frame.

A higher awareness of the problem and the widespread use of more reliable and sensible diagnostic tools, especially echocardiography, could certainly also explain a “false” increase in the incidence and prevalence of HF.

Figure 5A shows the hospitalization rates for congestive HF in USA over a span of 35 years. For people younger than 65 years, HF prevalence increased from 1971 to 1993 and remained stable until 2006. Rates for those 65 years and older increased from 1970 to 1998 and remained somewhat stable until 2006. In contrast, hospital mortality has progressively decreased during the last 25 years, contributing to the observed increase in the prevalence of HF (Figure 5B).

Table I. The heart failure pandemic in numbers.

- 26 million people with HF worldwide
- 6.5 million people with HF in Europe
- 600 000 new HF cases per year in Europe
- 5.8 million American adults suffer from HF
- 500 000 new HF cases per year in the USA
- 1 in 5 adults over 40 years will have HF in their lifetime
- 1 in 5 HF patients die within 1 year
- 6- to 9-fold increase in sudden death in HF compared with the normal population
- 3 major risk factors for HF are currently on the increase: age, diabetes, and obesity
- 2.8% prevalence of HF in the USA in 2010, will increase to 3.5% by 2030
- $24.7 billion cost of HF in the USA in 2010, will increase to $77.7 billion by 2030

Figure 4. Low left ventricular ejection fraction in normal individuals with previously unknown heart disease.
Left ventricular ejection fraction <30% in normal individuals with previously unknown heart disease, of whom about 50% were completely asymptomatic.
Despite an increasing prevalence, the majority of evidence indicates that the incidence of HF has plateaued and might even be decreasing in some groups. In Western countries, including Canada, the USA, and countries in Western Europe, the incidence and prevalence of HF as well as the hospital admissions for HF has decreased during the last decade when corrected for age. This trend has not been observed in many other countries where the prevalence of heart disease remains very high (as in Eastern European countries) or is still increasing (as in some Asian and South American countries).

What is expected in future years is controversial and depends mostly on the success we have in controlling risk factors and on the change in life expectancy of the population. Most estimates predict a steady increase in the total number of cases, even in countries where cardiovascular diseases and cardiovascular mortality is declining. Again, the aging of the population explains the otherwise contradictory epidemiologic predictions. Table II shows the predicted prevalence of HF, as well as the direct costs (medical care, hospitalization, treatments) and the indirect costs (loss of productivity) attributed to HF, for the years 2010 to 2030 in the United States. The increase in prevalence will be relatively small, but over a 20-year period is equivalent to 25%, a figure that implies a terrible social and economic burden, with a cost increase of over 200%. These estimates may be conservative; if changing lifestyles lead to an increase in risk factors that have a strong impact on HF, such as diabetes and obesity, we may see an even greater increase in cardiovascular diseases and HF and their associated costs.

In countries with an economy in transition, the possibilities are even more dramatic. The control of communicable diseases, the

### Table II

<table>
<thead>
<tr>
<th>Year</th>
<th>Prevalence of HF (%)</th>
<th>Direct costs of HF ($ billions)</th>
<th>Indirect costs of HF ($ billions)</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>Overall change (%)</td>
<td>25.0</td>
<td>215</td>
<td>80</td>
</tr>
</tbody>
</table>

*Table II. Projections of heart failure prevalence and the direct and indirect costs of heart failure in the United States from 2010-2030. Direct costs are medical care, hospitalization, and treatments, while indirect costs include loss of productivity. Based on data from the American Heart Association Advocacy Committee in reference 32.*
expected step increase in life expectancy, and the changes in lifestyle (mainly due to a shift from rural to urban communities) may lead to a steady increase in cardiovascular diseases and HF, causing a pandemic that will be, put simply, global. The only hope is in the control of risk factors.

Preventing an epidemic outbreak

**Risk factors**

A number of risk factors, such as ischemic heart disease, hypertension, smoking, obesity, atrial fibrillation, diabetes, and tachycardia, among others, have been identified to both predict the incidence of HF as well as its severity.11,36-39

The risk of HF is particularly high in coronary disease (the incidence of HF is highest after myocardial infarction) and diabetes. Needless to say, prevention of cardiovascular diseases, changing lifestyle and diet (or maintaining healthy lifestyles and diets in some populations), and using appropriate medications are the best and most rewarding strategies to control the growing medical, social, and economic burden of HF.

**Role of the patient**

HF is a chronic disease, and the role of the patient in prevention and treatment is crucial. Although the awareness of the problem of HF is very low,41 the majority of citizens from developed countries are aware of the negative effects of major classic risk factors, such as obesity, hypercholesterolemia, smoking, hypertension, sedentary lifestyle, etc. In spite of this awareness, the control of some factors is lower than expected,41,42 while others are clearly increasing, especially obesity and diabetes, both of which are related to modern lifestyles and HF. Education and legislation will be crucial to control the growing global burden of cardiovascular heart diseases, HF included.^1^

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Keywords: heart failure; epidemic; life expectancy; prevention; risk factor

L’INSUFFISANCE CARDIAQUE COMME ÉPIDÉMIE

L’insuffisance cardiaque représente un important problème médical, social et économique. Bien que des estimations fiables manquent dans de nombreux pays, sa prévalence est estimée à 2 à 3 % de la population adulte et augmente avec l’âge. Plus de 26 millions de personnes souffrent d’insuffisance cardiaque dans le monde et plus de 3,5 millions de nouveaux cas sont diagnostiqués chaque année dans la seule Europe. Le pronostic à long terme de l’insuffisance cardiaque est pire que celui de la plupart des cancers, avec une mortalité de 50 % à 4 ans. Les patients souffrent de symptômes handicapants souvent réfractaires au traitement et nécessitant une hospitalisation, dont l’impact sur la qualité de vie est très négatif comparé à d’autres maladies chroniques. Le coût des soins médicaux se chiffre en milliards de dollars. La prévalence de l’insuffisance cardiaque a augmenté progressivement à partir du début des années 50 et pendant 30 ans pour finalement atteindre un plateau. Il est cependant probable qu’une nouvelle augmentation apparaîsse en raison du vieillissement de la population et de la prévalence croissante de facteurs de risque cardiaques comme l’obésité et le diabète. Tous les pays, mais surtout ceux en période de transition économique dont les modes de vie traditionnels sont en plein bouleversement, sont confrontés au défi de la prévention. Cette dernière est la seule façon d’éviter une véritable pandémie d’insuffisance cardiaque, et incombe tant aux médecins, aux administrations de la santé et de l’éducation, qu’aux patients eux-mêmes.
In the United States, heart failure continues to be the most common cause of hospitalization in people older than 65 years of age, with a reported 26% rise in hospital discharge rates from 877,000 in 1996 to 1,106,000 in 2006. In Europe, 5% of adult internal medicine and geriatric hospitalizations occur as a result of heart failure—a larger proportion than those that occur as a result of myocardial infarction.”

Clinical and economic burden of chronic heart failure

by M. R. Cowie, United Kingdom

Around 2% of the adult population in the developed world have heart failure (HF), the prevalence of which rises steeply with age. Male gender, advanced age, more severe symptoms, coronary artery disease (particularly acute coronary syndrome), hypotension, impaired renal function, hyponatremia, and elevated plasma brain natriuretic peptide concentration are all factors associated with poorer prognosis. In Europe, HF accounts for 5% of adult internal medicine and geriatric hospitalizations, and the median duration of hospitalization is 11 days. Readmission rates are high, with one third to one half of patients being readmitted within 12 months. Although the prognosis of the syndrome is still severe, available data suggest that it is improving even though it remains worse than that of many common malignancies. The improving prognosis, coupled with a rapidly aging population, is driving a steep increase in the total number of people with HF: conservative estimates suggest that 6 million Europeans have this syndrome. It is a costly condition to treat: between 1% and 2% of national health care budgets are spent on HF, with more than 60% of this cost related to hospitalization. The condition has a major impact on many aspects of an individual’s quality of life, which is regarded as being worse in HF than in chronic lung disease, arthritis, or diabetes.

The epidemiology of heart failure (HF), and its impact on health services, has been well described, at least for the developed world. Published studies, which have used a range of methodologies, have been supplemented by data from surveys of hospital practice in North America and Europe. The literature on quality of life in HF is limited, but suggests that the syndrome has a major impact on many aspects of daily life.

Incidence

Reliable estimates of the incidence of HF are available from studies such as the Framingham Heart Study in the United States,” and the Hillingdon and Bromley Heart Failure Studies in London, UK.” The Framingham Study employed set criteria at biennial examinations of a cohort of individuals initially free of HF. The London studies employed an expert panel approach that reviewed all the available data for those with a new diagnosis of HF within a geographically defined population, using a systematic method of assessment that included imaging of the heart by Doppler echocardiography. Table I summarizes the results of these and other key incident studies.”
H E A R T F A I L U R E T O D A Y: A P A R A D I G M S H I F T

Clinical and economic burden of chronic heart failure – Cowie

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The crude incidence rate in the general population ranges from 1 to 5 cases per 1000 population per year, with a steep increase with advancing age: the annual incidence is estimated to be 0.2%-0.3% in those aged 50-59 years; in those aged 80-89, this rises tenfold (Figure 1). The median age at first presentation in most recent studies (in the developed world) is the mid-70s, with a higher incidence in men than in women at all ages (male:female ratio is \(\approx 1.8:1\)). It is not clear whether the incidence of HF has changed in the past few decades. The Framingham Heart Study reported no change during the period from 1950 to 1999 for men, but a small decrease in the early stages of HF during the same period for women. Elsewhere, data from Olmsted County, Minnesota, showed no change in the incidence of HF from 1979 through 2000, while the Kaiser Permanente database in the Pacific Northwest of the United States suggests an increase of 14% in the HF incidence rate between 1970 and 1994.

### Prevalence

Studies from both Europe and North America suggest that the prevalence of HF is approximately 2% of the adult population, with a steep rise with age. Few adults aged younger than 40 years of age have HF. Early studies used a range of methods to estimate prevalence, including medical record reviews that were supplemented by direct questioning and/or examination of individuals within the general population, drug prescription data analysis, monitoring of general practice activity, and appropriately sampled cohorts from the general population. The results of some key studies are shown in Table II (page 372).

The first population-based study to use two-dimensional Doppler echocardiography was in Glasgow, UK. The prevalence of HF was reported as 1.5% in 1647 participants aged 25 to 74 years. The definition of HF was left ventricular ejection fraction (EF) less than 30% and cardiac shortness of breath on questionnaire or use of a loop diuretic. Asymptomatic left ventricular systolic dysfunction was almost as common as HF, at 1.4% in this population. A population-based study in Rotterdam, The Netherlands, reported a prevalence of HF of 0.7% in those 55 to 64 years of age, 2.7% at 65 to 74 years of age, 13% at 75 to 84 years of age, and over 10% in those 85 years of age or older. A trained nonmedical interviewer administered a standardized questionnaire, a clinician detected pulmonary rales and ankle edema in a subsample of individuals, and an electrocardiograph and echocardiogram were recorded. HF was considered present if the individual did not have chronic pulmonary disease, but had evidence of cardiac disease and at least two of the following three characteristics: history of dyspnea, ankle edema, or pulmonary rales.

### Table I. Incidence of heart failure in a selection of population-based studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cowie et al, Hillingdon, 25-34 y</td>
<td>0</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>London, 1995-1996</td>
<td>1.7</td>
<td>0.7</td>
<td>1.2</td>
</tr>
<tr>
<td>65-74 y</td>
<td>3.9</td>
<td>2.3</td>
<td>3.0</td>
</tr>
<tr>
<td>75-74 y</td>
<td>9.8</td>
<td>5.9</td>
<td>7.4</td>
</tr>
<tr>
<td>85+ y</td>
<td>16.8</td>
<td>9.6</td>
<td>11.6</td>
</tr>
<tr>
<td>Framingham, USA, 50-59 y</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>60-69 y</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>1948-1988</td>
<td>12</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>80-89 y</td>
<td>27</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Rochester, USA</td>
<td>1979-1984</td>
<td>3.6</td>
<td>2.8</td>
</tr>
<tr>
<td>1985-1990</td>
<td>3.9</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>1991-1995</td>
<td>3.8</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>1996-2000</td>
<td>3.8</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Framingham, USA</td>
<td>1950-1969</td>
<td>6.3</td>
<td>4.2</td>
</tr>
<tr>
<td>1970-1979</td>
<td>5.6</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>1980-1989</td>
<td>5.4</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>1990-1999</td>
<td>5.6</td>
<td>3.3</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Incidence of heart failure by age group and gender in the Hillingdon Heart Failure Study, London, from 1995 to 1997 (cases per 1000 population per year).

Selected abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF</td>
<td>ejection fraction</td>
</tr>
<tr>
<td>HF</td>
<td>heart failure</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
</tbody>
</table>
Definite HF, defined as individuals who were breathless on exertion and who had objective evidence of underlying cardiac dysfunction, such as EF <40%, atrial fibrillation, or moderate-to-severe valve disease, was present in 2.3% of the general population 45 years of age and older in Birmingham, UK.15 Probable HF was reported in a further 0.8%.

In North America, several studies have reported similar figures, including the Cardiovascular Health Study16 and the National Health and Nutrition Examination Survey.17 In Olmsted County, Redfield and colleagues recently reported a prevalence of 2.2% in the population aged 45 years or older, applying the Framingham criteria to data in community- and hospital-based medical records.18 Of the 45 participants with a validated diagnosis of HF, 20 (44%) had an EF ≥50%. The prevalence of HF increased steeply with age: 0.7% for those 45 to 54 years of age; 1.3% in those 55 to 64 years of age; 5% in those 65 to 74 years of age; and 8.4% for those 75 years of age or older.

On the basis of these studies, a conservative estimate of the burden of HF would be that 4 million Americans and 6 million Europeans have HF out of a total population of 300 million and 460 million, respectively.

**Prognosis**

Despite the current use of life-prolonging therapies, such as angiotensin-converting enzyme inhibitors, β-blockers, and aldosterone receptor antagonists, a new diagnosis of HF carries a prognosis similar to that of bowel cancer, which is worse than that of breast cancer.19,20 The comparative survival from HF and a variety of malignancies in the United States is shown in Figure 2.21,22 Factors associated with a poorer prognosis include male gender, advanced age, more severe symptoms (higher New York Heart Association [NYHA] class), coronary artery disease (particularly acute coronary syndrome), hypotension, impaired renal function, hyponatremia, and elevated plasma BNP concentration.19,23-25

The overall in-hospital mortality for patients admitted with HF is between 4% and 7%.26 Those presenting with cardiogenic shock (low cardiac output with organ hypoperfusion) have a particularly high in-hospital mortality of ≈40%. Within 12 weeks of initial discharge, 1 in 4 acute HF patients are readmitted to hospital and ≈15% are dead, rising to 30% at 12 months from discharge. Death is most likely to occur due to progressive HF in the more severe grades of HF (often after several decompensations requiring hospitalization), but...
sudden death can occur at any time. Predicting likely life expectancy is more difficult than in terminal malignancies, making management decisions more difficult. Although HF prognosis is today better than it once was, the long-term mortality rate remains high.

Figure 3 shows long-term survival in a cohort of 552 new cases of HF identified in the London Heart Failure Studies from 1995 to 1998. The survival of incident cases was similar in the Rotterdam Study, with 1-, 2-, and 5-year survival rates of 63%, 51%, and 35%, respectively.27 Mortality is particularly high in the 3 months after diagnosis. The most recent data from the Framingham Heart Study shows a similar picture, but with evidence of improvement in prognosis in the past 30 years (Figure 4).9 Recent epidemiological data from the Olmsted County Rochester Epidemiology Project11 and the United Kingdom confirm this improvement.28,29

This is expected to rise to 16.3% in 2020, 19.6% in 2030, and 22.4% in 2040.30 Similar population projections have been made for Europe.31

Temporal trends in heart failure

The number of people living with HF in Europe and North America is set to increase steeply. The rapid aging of the population in developed countries, lack of a fall in incidence, and improving prognosis of HF are all acting to increase the number of people with chronic HF—with no likely decrease anticipated in the near future. In 2002, 12.6% of the population was older than 65 years of age in the United States.30 Similar population projections have been made for Europe.31

Health-care burden

In the United States, HF continues to be the most common cause of hospitalization in people older than 65 years of age,22,32 with a reported 26% rise in hospital discharge rates from 877 000 in 1996 to 1 106 000 in 2006. In Europe, 5% of adult internal medicine and geriatric hospitalizations occur as a result of HF—a larger proportion than those that occur as a result of myocardial infarction.33 The age-adjusted rates for hospitalization may have peaked.34 The duration of hospitalization for HF, particularly in Europe, is long with a median duration in the Euroheart Heart Failure survey of 11 days.35 The typical duration of hospitalization in the United States is closer to 5 days.36,37

Figure 3. Cumulative survival of the 552 individuals with incident (new) heart failure identified in the Hillingdon and Bromley (London) Heart Failure Studies from 1995 to 1998. The expected survival curve represents the age- and gender-matched UK population. Observed survival is shown with 95% confidence interval limits. Based on the author’s own data.

The readmission rate is also high, with one third to one half of patients being readmitted within 6 months in the United States\(^3\). Mortality after hospitalization is also high, with 13% dying within 12 weeks in Europe.\(^3\) Not all admissions are as a result of HF, but 20% to 50% of the emergency readmissions are likely to be so,\(^3\) with some patients being readmitted multiple times.

Hospitalization is the main driver of the cost of HF to the health service. Approximately 60% of the total direct costs of HF relate to hospitalization, 1% to 2% of the total health care budget of many developed countries.\(^22,23\) Added to the direct health care costs are the economic consequences of HF to patients and their families: the total (direct and indirect) cost of HF was estimated to be $39.2 billion in the United States for 2010.\(^22\)

From an individual perspective, the diagnosis of HF is associated with annual costs of approximately $8500 per patient according to data from the National Heart and Lung Institute cardiovascular health study.\(^23\) These estimates may underestimate the real costs as they are based on data featuring HF as the primary diagnosis; HF treatment costs also need to be taken into account for the many patients primarily hospitalized for one of the multiple comorbidities that typically accompany HF, such as hypertension, diabetes, and renal or lung disease. Whellan et al.\(^24\) studied almost 1.4 million Medicare beneficiaries after their initial hospitalization for HF and found that 66% made a subsequent in-patient claim the following year. HF hospitalizations accounted for 15% of total in-patient costs, while 57% of costs were associated with noncardiovascular diagnoses.

**Quality of life**

HF has a major impact on many aspects of health-related quality of life. Studies from Europe have reported that people with HF have more severe physical impairment than those with chronic lung disease, arthritis, or diabetes and similar impairment to those with Parkinson’s disease or motor neuron disease (Figure 5).\(^43-45\)

**Figure 5.** Forest plot showing the mean EuroQoL (EQ-5D index) score of patients enrolled in the CARe-HF study compared with the mean EuroQol scores of patients with other chronic diseases and those of a sample of the UK population.

**Abbreviations:** CARe-HF, Cardiac Resynchronization in Heart Failure.; EQ-5D, EuroQol 5 Dimension [mobility, self-care, usual activities, pain/discomfort, anxiety/depression health survey].


HF affects mobility and the ability to carry out usual activities. Mental health is affected, but less so than in patients with depression, although this can often coexist in patients with HF.\(^43,46\) Assessment of quality of life is not routine in clinical practice, although NYHA class appears to correlate relatively closely with overall health-related quality of life, as assessed by the Short Form-36 questionnaire.\(^46\) Work from the United States\(^47\) suggests that a disease-specific questionnaire (the 23-item Kansas City Cardiomyopathy Questionnaire) is more sensitive to changes in overall clinical condition, than the EQ-5D (a more generic, and much simpler, quality of life instrument).\(^46\) or NYHA class. Narrative meta-analysis of the small number of published qualitative studies of HF suggests that social isolation, living in fear, and the loss of a sense of control are very common consequences of HF.\(^49\)

**Conclusions**

HF remains a major public health issue that is likely to increase in importance as the world’s population ages and survival from the syndrome continues to improve. The already huge cost of delivering care is also likely to increase. At a personal level, a diagnosis of HF will have an important impact on the individual’s length and quality of life, particularly where chronic disease management is poor.
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Keywords: heart failure; epidemiology; economics; quality of life

Clinical and economic burden of chronic heart failure – Cowie
Environ 2 % de la population adulte des pays développés souffrent d’insuffisance cardiaque (IC) dont la prévalence augmente rapidement avec l’âge. Les facteurs de mauvais pronostic incluent: sexe masculin, âge avancé, symptômes plus sévères, coronaropathie (surtout syndrome coronaire aigu), hypotension, insuffisance rénale, hyponatrémie et concentration plasmatique élevée en peptide cérébral natriurétique. En Europe, l’IC représente 5 % des hospitalisations en gériatrie et en médecine interne adulte, la durée moyenne d’hospitalisation étant de 11 jours. Les taux de réhospitalisation sont élevés, un tiers à la moitié des patients étant réhospitalisés dans l’année. Bien que le pronostic demeure encore sévère, les données disponibles semblent indiquer qu’il amorce une amélioration, tout en restant moins bon que celui de nombreuses pathologies malignes courantes. L’amélioration du pronostic associé au vieillissement rapide de la population explique l’augmentation dramatique du nombre total d’insuffisants cardiaques : des estimations prudentes indiquent que 6 millions d’Européens sont atteints de ce syndrome. Le coût de traitement de la maladie est important : entre 1 et 2 % des budgets nationaux de santé, plus de 60 % de ce coût étant lié à l’hospitalisation. L’IC a un impact majeur sur nombre d’aspects de la qualité de vie, celle-ci étant bien plus altérée que dans les pneumopathies chroniques, l’arthrose ou le diabète.
Observational research today, particularly in the form of surveys and registries, which are widely used by the clinical/scientific community, has several applications. Well-defined methodologies, which vary according to the specific aim(s) of the research, must be applied. This paper reports some observational findings on heart failure (HF) that were collected in a recent survey conducted by the European Society of Cardiology (ESC). This survey, with a multinational European network structure, was based on the principles of observational research. Its aim was to get a picture of real clinical profiles of both acute and chronic HF patients and to compare current therapeutic regimens in HF with ESC guideline recommendations. The main observations are as follows: (i) the clinical profiles of acute HF suggested by the ESC broadly identify small subsets of subjects with different outcomes, but this still leaves large clinical areas that are not fully characterized; (ii) acute HF therapy has remained practically unchanged in the last few decades, and we require proper randomized controlled trials for a better understanding of pathophysiological profiles; and (iii) although chronic HF therapy is evidence-based, drug doses currently used in clinical practice are far from recommended doses. In spite of these shortcomings, recently tested new drugs have been found to be both effective and safe, and with rapid incorporation in guidelines these should improve patient outcomes.

Medicographia. 2011;33:377-383 (see French abstract on page 383)
observational clinical study to obtain reliable and informative data are discussed. These criteria have been applied in the above-mentioned survey.

**General outline of a registry**

Some preliminary questions that should be answered before starting an observational study are listed and briefly commented on below (Table I).

**Table I. Preliminary questions that should be answered before starting an observational study.**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Which questions should the registry answer?</td>
<td>This is the preliminary, essential platform upon which the design and data set of a registry should be set up.</td>
</tr>
<tr>
<td>Are the patient enrollment criteria and the definitions of the variables to be collected clearly stated?</td>
<td>Large randomized controlled trials are usually planned with stringent protocols, clear definitions, and cogent inclusion/exclusion criteria. Protocols of observational studies may be less precise and exposed to major risks of misunderstanding or unintended violations. The current registries on acute HF may be a pertinent example. In Table II, the in-hospital mortality rates recorded in recent surveys and registries enrolling patients diagnosed as having acute HF are reported. The mortality rates range from 1.8% to 24%. A number of reasons may account for such huge differences, but probably the main reason is the vagueness of the diagnosis criteria of acute HF, which makes the populations different and noncomparable.</td>
</tr>
<tr>
<td>Is the sample of subjects enrolled representative of the population of interest?</td>
<td>This essential issue depends on both the representativeness of the network of enrolling centers and the consecutiveness of patient enrollment. Observational studies are mainly voluntary, and all centers willing to participate are generally welcome. This implies that the types of centers included in the study network may not be representative of the real network of centers existing in a region, country, or continent where the study is performed, in terms of geographical distribution, organization, admitted patients, availability of diagnostic and therapeutic technology, or other characteristics. This may make the external consistency of the collected data uncertain and questionable.</td>
</tr>
<tr>
<td>Are data quality controls planned?</td>
<td>Both central quality control of the data and peripheral auditing at enrolling centers should be performed. This is a costly, but essential process.</td>
</tr>
<tr>
<td>Are the sample size and analytical plan predefined?</td>
<td>The assumptions on which both the size and duration of observational studies are founded are frequently hypothetical and conceptually not as stringent as those of RCTs. However, they should be predefined.</td>
</tr>
<tr>
<td>Does the registry include incident patients, known patients, or both?</td>
<td>This is a critical decision to take. An “all comers” strategy is exposed to the bias of mixing survivors of previous events and new patients with a potentially different probability of surviving. The same consideration applies to drug users. Patients taking a drug are not only survivors, but are tolerant to the drug and compliant. On the other hand, including only patients at first diagnosis may lead to the selection of patients with acute events.</td>
</tr>
<tr>
<td>Is the study “independent”?</td>
<td>Surprisingly, there is a diffuse belief that observational research is low cost and easy to perform. This is wrong and it is a source of either poor studies or a lot of frustration. However, a study can be claimed to be independent if conceived and coordinated by independent investigators, the database is in their hands, and they are owners of the data. Such neutral networks of research should be implemented under the guidance and responsibility of independent bodies.</td>
</tr>
</tbody>
</table>

**Table II. In-hospital mortality registries.**

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients (years)</th>
<th>Hospital stay (days)</th>
<th>In-hospital mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPTIMIZE HF</td>
<td>5751</td>
<td>72</td>
<td>1.6</td>
</tr>
<tr>
<td>IMPACT-HF</td>
<td>567</td>
<td>71</td>
<td>2.8</td>
</tr>
<tr>
<td>ADHERE</td>
<td>65,000</td>
<td>72</td>
<td>4</td>
</tr>
<tr>
<td>Goldberg</td>
<td>2604</td>
<td>79</td>
<td>4.1</td>
</tr>
<tr>
<td>European HFS 2</td>
<td>3580</td>
<td>70</td>
<td>6.7</td>
</tr>
<tr>
<td>Italian AHFS</td>
<td>2807</td>
<td>73</td>
<td>7.3</td>
</tr>
<tr>
<td>FINN-AKVA</td>
<td>620</td>
<td>75</td>
<td>8</td>
</tr>
<tr>
<td>Rudiger</td>
<td>312</td>
<td>73</td>
<td>8</td>
</tr>
<tr>
<td>European HFS 1</td>
<td>11,327</td>
<td>71</td>
<td>8.4</td>
</tr>
<tr>
<td>EFFECT</td>
<td>4031</td>
<td>76</td>
<td>8.9</td>
</tr>
<tr>
<td>Argentina Reg</td>
<td>2974</td>
<td>65-70</td>
<td>4-12</td>
</tr>
<tr>
<td>EFICA</td>
<td>599</td>
<td>73</td>
<td>27/43 (4 weeks)</td>
</tr>
</tbody>
</table>

Observational research in heart failure – Tavazzi
fertent types of cardiology facilities (with or without cardiac surgery and interventional facilities). The aim of this selection was to provide an up-to-date picture of HF in Europe by establishing a network with a broad spectrum of cardiology units capable of consecutively enrolling and following outpatients with HF and admitting patients with acute/worsening HF. From October 2009 to May 2010, 5118 patients were included in a pilot phase of this registry, and follow-up is ongoing. A few of the findings recorded at the enrollment of these patients, which are worthy of further consideration, are discussed below.1

**Hospital in-patients**

Some 1892 patients were admitted to hospital for acute/worsening HF. Mean age was 70 years, and about a third of the patients enrolled were female. More than half of the patients (64%) had an ischemic etiology confirmed by coronary angiography. At hospital entry, either pulmonary or peripheral congestion was detected in 82% of cases, and clinical signs of peripheral hypoperfusion were reported in 9% of the patients.

Atrial fibrillation was detected in 35% of the patients as well as a large QRS (≥120 ms). An echocardiographic examination was performed in 75% of the patients. The median ejection fraction (EF) was 38% (interquartile range [IQR] 27%-52%); 39% of the patients had preserved EF, defined as EF >40%. Moderate-to-severe mitral regurgitation was diagnosed in 43% of the patients. Echocardiograms were performed during hospitalization, but not necessarily on admission. As a result, we do not know what the EF value was when the clinical status of the patient was at its worst. However, the proportion of patients with preserved or mildly compromised ventricular systolic function observed in this cohort of acute or worsening HF patients (approximately 40%) is similar to that found in other comparable surveys, confirming that a drop in ventricular systolic contractile performance is not necessarily the precipitating cause of decompensation.

Comorbidities were frequent. Anemia, defined as a hemoglobin level <12 g/dL, was detected in 31% of patients; an estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m² and <30 mL/min/1.73 m² was reported in 33% and 10% of patients, respectively. Over a third (35%) of patients had a history of diabetes, while 54% had hyperglycemia on admission.

N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP) were measured at entry in 489 and 204 patients only. The median values were 4007 pg/mL (IQR 2043-9487 pg/mL) and 870 pg/mL (IQR 423-1950 pg/mL), indicating the severity of patients’ clinical condition at hospital admission. Troponin (I or T) was measured in 987 patients with a median value of 0.04 ng/mL (IQR 0.01-0.29 ng/mL). These important markers of ventricular stress and compromise have not so far been fully incorporated in clinical practice.

The definition of acute HF reported in international guidelines is quite vague, which has led to the inclusion of heterogeneous populations under the umbrella of “acute heart failure.” This is one of most important reasons for the failure to have developed active drugs in the setting of acute HF, as most RCTs adopted an “all comers” approach. The current European guidelines for the diagnosis and treatment of HF propose a stratification of patients admitted for acute HF.

![Figure 1A](page 380) shows the stratification of patients enrolled in the ESC-HF (European Society of Cardiology Heart Failure) survey, according to the clinical profiles in the ESC guidelines.2 Decompensated HF was most frequent clinical profile (75% of the cases), while pulmonary edema and cardiogenic shock were reported in 13% and 2% of patients, respectively. Figure 1B shows the overall rate of in-hospital mortality stratified by clinical profile. As expected, patients with cardiogenic shock have the worst short-term prognosis. For this reason, patients presenting with this clinical profile should be managed with specific, intensive approaches. Patients with hypertensive HF are the other extreme, showing the most favorable in-hospital survival.

It is unlikely that the inclusion of both these patient categories in the same trial testing the same drug could lead to meaningful and applicable results. Whether the category of “decompensated heart failure” (75% of patients) represents a homogeneous group of patients is difficult to envisage, and to believe. There is the need, in future, to better clarify the relationship between clinical pictures and the definitions of profiles suggested by the guidelines to obtain a patients’ categorization that allows both individual decision-making and the identification of patient populations appropriate for testing specific new drugs.

Overall, 71 patients died during their hospital stay. When age and two major markers of cardiovascular function (systolic blood pressure and reduced renal function) were considered,
93% of deaths could be explained by the presence of at least one of these factors. The median length of hospitalization was 8 days (IQR 5-11 days), and 48% of patients were managed in the intensive care unit for a median of 4 days (IQR 2-7 days). The median body weight reduction during the hospital stay was 2 kg. At discharge, pulmonary congestion, peripheral congestion, or both were still present in 10%, 18%, and 24% of cases, respectively.

The mean duration of hospitalization, compared to that recorded in a previous ESC survey on acute HF,4 was shortened by a day (from 9 to 8 days). The length of hospitalization in Europe remains approximately twice the length of hospitalization reported in US surveys.8,9 However, the number of patients showing clinical signs of congestion at discharge is still elevated and may account, at least in part, for the high rates of hard events and rehospitalizations observed in the few months after discharge in previous studies.10,11

Intravenous diuretics were used in 85% of cases. The median dose of furosemide used during the hospital stay was 60 mg per day (IQR 40-100 mg per day). Nitrates and inotropes were administered in 18% and 10% of patients. Of the inotropes, the most used was dobutamine (in 4.6% of patients) followed by levosimendan (in 2.4% of patients). In fact, in spite of many trials testing a number of new drugs in acute HF patients in the last decade, these patients are still treated in the same way today as the same patients were 20 years ago.

**Chronic heart failure in outpatients**

In this population (3226 patients enrolled), the rates of moderate (New York Hospital Association [NYHA] class I-ll) and severe HF (NYHA class III-IV) were 72% and 28%, respectively. Ischemic etiology accounted for just 40% of cases, with angiographic confirmation in 85% of cases. EF was available for 2857 patients (89%): its median value was 36% (IQR 30%-46%) and preserved EF (>40%) was reported in 36% of cases, a figure not far from that observed in patients with acute/worsening HF. A hemoglobin level <12 g/dL was reported in 19% of cases, and an eGFR <60 and <30 mL/min/1.73 m² was reported in 41% and 5% of patients. NT-proBNP and BNP were measured in a minority of cases (747 and 285 patients). Median values were 1387 pg/mL (IQR 485-3381 pg/mL) and 390 pg/mL (IQR 133-870 pg/mL).

The use of pharmacological treatments is reported in Table III.

**Table III.** Prescribed pharmacological treatment for chronic heart failure (n=3226 patients).

<table>
<thead>
<tr>
<th>Type of drug(s)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>83</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>65</td>
</tr>
<tr>
<td>ARBs</td>
<td>27</td>
</tr>
<tr>
<td>ACE inhibitors/ARBs</td>
<td>88</td>
</tr>
<tr>
<td>ß-Blockers</td>
<td>87</td>
</tr>
<tr>
<td>Digitalis</td>
<td>21</td>
</tr>
<tr>
<td>Aldosterone blockers</td>
<td>44</td>
</tr>
<tr>
<td>Nitrates</td>
<td>16</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>48</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>43</td>
</tr>
<tr>
<td>Statins</td>
<td>54</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>10</td>
</tr>
<tr>
<td>CCB</td>
<td>10</td>
</tr>
</tbody>
</table>
Observational research in heart failure – Tavazzi

Table IV. Doses of evidence-based treatments used in the ESC-HF Pilot Survey with respect to the recommended target doses.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Use (%)</th>
<th>Median dose (mg/day), IQR</th>
<th>stay (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors and doses (n=2078)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramipril</td>
<td>50.1</td>
<td>5 (3.75-10)</td>
<td>38.2% (10 mg/day)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>27.8</td>
<td>10 (10-20)</td>
<td>46.2% (20 mg/day)</td>
</tr>
<tr>
<td>Other ACE inhibitors</td>
<td>22.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ARBs and doses (n=864)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>34.7</td>
<td>16 (8-32)</td>
<td>28.0% (32 mg/day)</td>
</tr>
<tr>
<td>Losartan</td>
<td>26.4</td>
<td>50 (25-50)</td>
<td>19.7% (100 mg/day)</td>
</tr>
<tr>
<td>Valsartan</td>
<td>25.7</td>
<td>160 (80-160)</td>
<td>16.7% (320 mg/day)</td>
</tr>
<tr>
<td>Other ARBs</td>
<td>13.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>β-Blockers and doses (n=2774)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td>42.8</td>
<td>25 (12.5-50)</td>
<td>37.3% (50 mg/day)</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>32.3</td>
<td>5 (2.5-7.5)</td>
<td>20.7% (10 mg/day)</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>18.9</td>
<td>100 (50-150)</td>
<td>21.4% (200 mg/day)</td>
</tr>
<tr>
<td>Other β-blockers</td>
<td>6.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aldosterone antagonists and doses (n=1396)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>59.7</td>
<td>25 (25-25)</td>
<td>22.2% (50 mg/day)</td>
</tr>
<tr>
<td>Canrenone</td>
<td>27.3</td>
<td>50 (25-50)</td>
<td>61.3% (50 mg/day)</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>10.5</td>
<td>25 (25-50)</td>
<td>32.7% (50 mg/day)</td>
</tr>
<tr>
<td>Other aldosterone antagonists</td>
<td>2.5</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

We know that patients enrolled in clinical trials according to a number of inclusion/exclusion criteria represent a small, selected portion of the universe of HF patients. Moreover, the RCTs that tested recommended drugs against placebo were performed many years ago, with a background therapy that was markedly different to that which is currently used. The target doses recommended today were defined in those trials, which were not validated afterwards. Maybe, contrary to our expectations, these doses are not optimal for many patients.

This may particularly be the case for β-blockers. The history of β-blocker implementation is represented in Figure 2 (page 381), showing data recorded in a long-term Italian registry since 1995. Gradually, the prescription of the β-blockers increased until now about 80% of patients are taking these drugs. However, the doses have remained unchanged, at about one third of those recommended. A recent instructive experience occurred during SHIFT (Systolic Heart failure treatment with the I inhibitor ivabradine Trial), which tested ivabradine, a pure bradycardic agent, versus placebo on top of recommended treatments, including β-blockers.

Because both ivabradine and β-blockers reduce heart rate, an important goal of the trial (both for safety and efficacy) was to investigate the tested drug—ivabradine—when added to the highest tolerated dose of β-blockers. All the investigators were kept aware of this important condition and they were encouraged to modulate the β-blocker dose according to guideline recommendations, and required to report the rea-
Interestingly, a similar dissociation between recommendations and clinical practice was noted in a European survey of electrical device implantation. According to current guidelines, 37% of patients had clinical characteristics that suggested an implantable cardioverter-defibrillator (ICD) was potentially suitable. Of these patients with a theoretical indication for the implant, only one third (33%) actually received an ICD implant. Similarly, of the 6% of patients with a clinical profile suitable for a CRT (cardiac resynchronization therapy) device, only 2.2% actually received an implant.

The ESC-HF survey commented on above provides a clear picture of the clinical profiles of both acute and chronic HF patients in Europe, the rate of use of guideline-recommend-


**Keywords:** observational research; heart failure

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**Recherche observationnelle dans l’insuffisance cardiaque**

La recherche observationnelle est aujourd’hui largement utilisée par la communauté clinique et scientifique, et fait appel en particulier aux études et aux registres. Elle est basée sur des méthodologies bien définies, qui varient selon le(s) but(s) spécifique(s) de la recherche. Cet article présente des résultats sur l’insuffisance cardiaque (IC) recueillis dans une récente étude observationnelle conduite par la Société Européenne de Cardiologie (ESC). Cette étude européenne, à structure multinationale en réseau, avait pour but de donner un aperçu des profils cliniques réels de l’IC aiguë et chronique et de comparer les schémas thérapeutiques actuels dans l’IC avec les recommandations de l’ESC. Les résultats principaux en ont été les suivants : 1) les profils cliniques de l’IC aiguë proposés par l’ESC définissent des petits sous-groupes de sujets aux évolutions différentes, tout en laissant encore de grands domaines cliniques incomplètement caractérisés ; 2) le traitement de l’IC aiguë est resté pratiquement inchangé ces 10 dernières années, et nous avons besoin d’études contrôlées randomisées bien conçues pour une meilleure compréhension des profils physiopathologiques ; et 3) bien que le traitement de l’IC chronique soit basé sur des preuves, les posologies actuellement utilisées en pratique clinique sont très éloignées des doses recommandées. Malgré ces faiblesses, de nouveaux traitements récemment testés s’avèrent à la fois efficaces et sûrs et devraient, après intégration rapide dans les recommandations, améliorer le devenir des patients.
Most trials have included only patients with left ventricular (LV) systolic dysfunction defined by an ejection fraction below 35% to 40%. Current drug therapy is based on our understanding of the pathophysiology behind heart failure progression... Drug therapy remains the mainstay of management. Its key objectives are symptom relief, slowing of disease progression (even reversal of myocardial dysfunction, if possible), and prolongation of survival."

The objective of this paper is to review the evidence provided by the major clinical trials that have yielded new advances in heart failure management. Heart failure is a major public health burden associated with high morbidity and mortality, frequent hospitalization, and substantial cost. Prevalence is increasing through the combined effects of an aging population and the efficacy of heart disease therapies, in particular the prolonged survival associated with coronary artery disease. The cornerstone of the pathophysiology of heart failure is the activation of key neurohormonal systems (renin-angiotensin-aldosterone system and sympathetic nervous system). Landmark trials have established renin-angiotensin-aldosterone blockade using angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone receptor blockers, along with sympathetic blockade using β-blockers, as the mainstays of current treatment, conferring significant morbidity and mortality benefit. Recently, the Systolic Heart failure treatment with If inhibitor ivabradine Trial (SHIFT) demonstrated that heart rate reduction with ivabradine added to adequate β-blockade improved clinical outcomes in patients with heart failure.

Medicographia. 2011;33:384-388 (see French abstract on page 388)

Heart failure is a common clinical syndrome dominated by signs and symptoms of fluid retention, even if many patients are asymptomatic. As the end stage of various cardiac conditions, it is associated with high morbidity and mortality, frequent hospitalization, and substantial socioeconomic cost. It affects an estimated 5 million Americans, with over 550 000 new patients being diagnosed annually, and a total of 15 million European patients, equivalent to 2% to 3% of the total population and 10% to 20% of the over-70s. Prevalence is increasing because of population aging and improved management of heart disease, in particular coronary artery disease.

Heart failure can be divided into two types, depending on whether it is associated with systolic dysfunction (the more studied variant) or diastolic dysfunction. However, some consider the distinction arbitrary. Most trials have included only patients with left ventricular (LV) systolic dysfunction defined by an ejection fraction (EF) below 35% to 40%. Current drug therapy is based on our understanding of the pathophysiology behind heart failure progression. This review focuses on the drug management of heart failure as recommended in current guidelines on the basis of the evidence garnered from pivotal trials, and it includes prevention of acute
Drug therapy remains the mainstay of management. Its key objectives are symptom relief, slowing of disease progression (even reversal of myocardial dysfunction, if possible), and prolongation of survival.

The management of heart failure patients is based on two main pathophysiological mechanisms: inhibition of the renin-angiotensin-aldosterone system and inhibition of the sympathetic nervous system. Current guidelines recommend a number of medications that improve patient symptoms, including angiotensin-converting enzyme (ACE) inhibitors, β-blockers, diuretics, digoxin, angiotensin II receptor blockers (ARBs) (in patients who cannot tolerate ACE inhibitors), and vasodilators, such as nitrates. Among these, some medications have been shown to improve survival, such as ACE inhibitors, β-blockers, ARBs, and in some subsets of patients spironolactone and eplerenone.

### Inhibition of the renin-angiotensin-aldosterone system

- **ACE inhibitors in heart failure and their effect on mortality**
  Several trials have shown ACE inhibitors to prolong survival in various disease stages ranging from severe heart failure to asymptomatic LV dysfunction.

- **CONSENSUS**
  The COoperative North Scandinavian ENalapril SUrvival Study (CONSENSUS) investigated the effect of adding enalapril 40 mg to diuretics, digitalis, and spironolactone, but not β-blockers, in 253 patients with severe heart failure. Enalapril improved symptoms and life expectancy compared with placebo, but had no impact on sudden cardiac death.

- **V-HeFT-II**
  The Vasodilator-Heart Failure Trial II (V-HeFT-II) randomized 804 men with New York Heart Association (NYHA) class II and III heart failure to receive enalapril 20 mg (n=403) or hydralazine/isosorbide dinitrate (n=401) for 2 years. Sudden death was 14% and mortality from progressive heart failure 12% in the enalapril group compared with 23% and 10% in the hydralazine/isosorbide dinitrate group.

- **SOLVD**
  The Studies Of Left Ventricular Dysfunction–Treatment (SOLVD-Treatment) randomized 2569 patients with NYHA class II to III heart failure and EF <35% to enalapril 20 mg or placebo. After an average of 41 months, there were 16% fewer deaths in the enalapril group (P=0.0036), primarily deaths attributed to progressive heart failure, and 26% fewer hospitalizations (P<0.0001). SOLVD-Prevention randomized 4228 asymptomatic patients with EF ≤35% to enalapril 2.5 mg-20 mg or placebo. At an average of 37 months, total mortality was 8% lower in the enalapril group (nonsignificant [NS]) and there were fewer deaths and hospitalizations due to heart failure (P<0.001).

- **Other trials**
  The Survival And Ventricular Enlargement (SAVE) trial with captopril, the Acute Infarction Ramipril Efficacy (AIRE) trial with ramipril, and the TRAndolapril Cardiac Evaluation (TRACE) trial with trandolapril all showed that ACE inhibition significantly improves survival and reduces morbidity and mortality due to major cardiovascular events in patients with heart failure and/or a low EF.

### 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>AIRE</td>
<td>Acute Infarction Ramipril Efficacy</td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin receptor blocker</td>
</tr>
<tr>
<td>CHARM</td>
<td>Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity</td>
</tr>
<tr>
<td>CHARM-Added</td>
<td>Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity in patients with LV dysfunction already taking ACE inhibitors</td>
</tr>
<tr>
<td>CHARM-Alternative</td>
<td>Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity in patients with LV dysfunction intolerant to ACE inhibitors</td>
</tr>
<tr>
<td>CiBiS-II</td>
<td>Cardiac Insufficiency Blisoprol Study II</td>
</tr>
<tr>
<td>CONSENSUS</td>
<td>COoperative North Scandinavian ENalapril SUrvival Study</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>Carvedilol Prospective Randomized Cumulative Survival Study</td>
</tr>
<tr>
<td>EF</td>
<td>ejection fraction</td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure</td>
</tr>
<tr>
<td>EPHEUSUS</td>
<td>Eplerenone Post-AMI Heart Failure Efficacy and SUrvival Study</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricular</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>RALES</td>
<td>Randomized ALdactone Evaluation Study</td>
</tr>
<tr>
<td>SAVE</td>
<td>Survival And Ventricular Enlargement</td>
</tr>
<tr>
<td>SENIORS</td>
<td>Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with heart failure</td>
</tr>
<tr>
<td>SHIFT</td>
<td>Systolic Heart failure treatment with I1 inhibitor Ivabradine Trial</td>
</tr>
<tr>
<td>SOLVD</td>
<td>Studies Of Left Ventricular Dysfunction</td>
</tr>
<tr>
<td>TRACE</td>
<td>TRAndolapril Cardiac Evaluation</td>
</tr>
<tr>
<td>Val-HeFT</td>
<td>Valsartan Heart Failure Trial</td>
</tr>
<tr>
<td>VALIANT</td>
<td>VAlsartan In Acute myocardial INFarction</td>
</tr>
<tr>
<td>V-HeFT</td>
<td>Vasodilator-Heart Failure Trial</td>
</tr>
</tbody>
</table>
The above trials were consistent in showing that ACE inhibitors should be the basis for therapy, along with a diuretic and digoxin as necessary, in all patients with symptomatic LV dysfunction, unless contraindicated or not tolerated. However, they also showed, and clinical experience has confirmed, that potassium and creatinine levels need to be monitored in patients receiving ACE inhibitors.

Treatment may be associated with side effects such as hypotension and cough. ARBs are an alternative to ACE inhibitors for patients who cannot tolerate an ACE inhibitor.

**Angiotensin II receptor blockers**

ARBs are indicated mainly in patients in whom ACE inhibitors are contraindicated. The key trials in this regard include the Valsartan Heart Failure Trial (Val-HeFT), which showed that valsartan significantly reduced the combined end point of mortality and morbidity and improved the signs and symptoms of heart failure versus placebo; the CHARM-Added trial (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity—in patients with LV dysfunction already taking ACE inhibitors), which revealed candesartan (target dose 32 mg/day) significantly improved outcomes versus placebo in patients already receiving an ACE inhibitor or β-blocker; the CHARM-Alternative trial (CHARM—in patients with LV dysfunction intolerant to ACE inhibitors), in which candesartan at the same target dose of 32 mg/day significantly reduced cardiovascular mortality and hospitalization for heart failure in patients unable to tolerate an ACE inhibitor; and the VALIANT trial (VALsartan In Acute myocardial Infarction), which found valsartan 160 mg to be as effective as captopril 150 mg in all-cause mortality in patients with myocardial infarction complicated by heart failure (the combination of valsartan plus captopril, however, provided no added survival benefit, serving only to increase the rate of adverse events).

**Aldosterone antagonists**

Aldosterone antagonists are recommended in patients with NYHA class III or IV heart failure associated with systolic dysfunction in the absence of hyperkalemia and renal dysfunction. The recommendation is based on three placebo-controlled trials: the Randomized ALdactone Evaluation Study (RALES) in class III and IV heart failure patients with systolic dysfunction (EF ≤35%), which reported a 30% reduction in the relative risk (P<0.001) of all-cause mortality in the group taking spironolactone; the Eplerenone Post-AMI Heart failure Efficacy and SUvival Study (EPHESUS) in a total of 6632 patients with low EF (≤40%), which showed reductions in all-cause mortality (P=0.008) and the combined end point of cardiovascular mortality and hospitalization for cardiovascular events (P=0.002) over a mean follow-up of 16 months; and, most recently, the Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure (EMPHASIS-HF), which confirmed the reductions observed in all-cause mortality (P=0.008) and cardiovascular mortality plus hospitalization for heart failure (P<0.001), only this time in patients with mild symptoms, over a median follow-up of 21 months (the trial was stopped prematurely according to prespecified rules).

**Inhibition of the sympathetic nervous system with β-blockers**

The European and American guidelines recommend β-blockers in symptomatic heart failure unless contraindicated or not tolerated. As with ACE inhibition, the recommendations are based on a number of large-scale randomized trials.

**US Carvedilol Heart Failure Trials Program**

In 1996, the US Carvedilol Heart Failure Trials Program was the first to demonstrate the benefit of added β-blockade in heart failure, with reductions versus placebo of 65% in overall mortality and 38% in the combined risk of death or hospitalization (both P<0.001), leading the Data and Safety Monitoring Board to recommend termination of the study before its scheduled completion.

**CIBIS-II**

The Cardiac Insufficiency Bisoprolol Study II (CIBIS II) randomized 2647 patients with class III to IV heart failure and EF ≤35% to bisoprolol 1.25-10 mg or placebo. The trial was stopped after the second interim analysis due to the lower overall mortality on bisoprolol (n=156 [12%] vs n=228 [17%] on placebo; P<0.0001), as well as significantly fewer sudden deaths and all-cause hospital admissions.

**COPERNICUS**

In 2002, the CarvedilOL ProspEctive RaNdomIzed CUmula-tive Survival (COPERNICUS) trial reported reductions versus placebo of 27% (P<0.00002) in the combined risk of death or hospitalization for a cardiovascular cause and of 40% in the number of days in hospital for heart failure (P<0.0001) after a mean 10.4 months in 1156 patients with severe heart failure randomized to carvedilol (3.125-50 mg target dose).22

**SENIORS**

The Study of the Effects of Nebivolol Intervention on Outcomes in Seniors with heart failure (SENIORS) addressed the hitherto neglected topic of the safety and efficacy of β-blockade in patients aged 70 years or older with a broad range of EF values. Over a mean duration of 21 months, the primary outcome (a composite of all-cause mortality or cardiovascular hospital admission) occurred in 31.1% of patients on nebivolol compared with 35.3% on placebo (P=0.039), leading the authors to conclude that β-blockade with nebivolol is safe and effective in elderly patients with heart failure.

**Heart rate reduction by sinus node inhibition**

In 1986, the Norwegian cardiologist John Kjekshus tested the hypothesis that the degree of potential benefit of β-blockade after myocardial infarction depends quantitatively on the re-
duction in heart rate it achieves. Exhauasitive and stringent re-
view of acute and long-term intervention trials revealed a re-
lation between the actual reduction in resting heart rate and the
percentage reduction in mortality in each trial (r=0.50, P<0.05). Kjekshus also uncovered a near-similar relation
between the reduction in resting heart rate and nonfatal reinfar-
cion (r=0.59, P<0.05).24

These studies set the theoretical stage for the development of
agents that would be devoid of the unwanted effects of β-
and calcium blockade. They would lower heart rate while hav-
ing little or no activity elsewhere in the body. First-in-class of
these pure heart rate–lowering drugs was ivabradine, a spe-
cific inhibitor of the I,f current in the sinoatrial node.25

SHIFT
The recent Systolic Heart Failure treatment with I,f inhibitor iva-
bradine Trial (SHIFT) randomized 6558 patients with moder-
ate-to-severe heart failure and systolic dysfunction (EF ≤35%) to
ivabradine or placebo.26 All patients received concomitant
guideline therapy with ACE inhibitors, ARBs, β-blockers, aldo-
sterone antagonists, and diuretics. The primary end point was
a composite of cardiovascular death and hospitalization for
worsening heart failure. Over a mean follow-up of 23 months,
793 patients in the ivabradine group (24%) had a primary end
point event compared with 937 (29%) of those taking place-
bo (P<0.0001). The effects were driven mainly by fewer hos-
pitalizations for worsening heart failure (P<0.0001) and fewer
deaths due to heart failure (P=0.014). The hazard ratio for car-
diovascular death or hospitalization for worsening heart fail-
ure was 18% lower than in the placebo group. Serious adverse
events rates were also fewer in the active treatment group
(P=0.025), leading the authors to conclude that ivabradine
was effective and well tolerated and should have an impor-
tant role to play in the treatment of heart failure in the future.

Conclusion
Insights into the fundamental mechanisms of heart failure, domi-
inated by activation of the renin-angiotensin-aldosterone
and sympathetic nervous systems, have driven the major ad-
vances in drug therapy achieved in recent decades, namely
the addition to therapy of ACE inhibitors, ARBs, and aldo-
sterone inhibitors, on the one hand, and β-blockers on the
other. More recently, a novel approach to reducing heart rate by
sinus node inhibition with ivabradine has been shown to im-
prove clinical outcomes and emphasizes the importance of
achieving adequate heart rate reduction in patients with heart
failure.

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Keywords: angiotensin-converting enzyme inhibitor; angiotensin receptor blocker; β-blocker; diuretic; heart failure; ivabradine; systolic dysfunction

**PRINCIPALES ÉTUDES DANS LES AVANCÉES DE LA PRISE EN CHARGE DE L’INSUFFISANCE CARDIAQUE**

Heart failure with reduced ejection fraction (EF) is associated with poor outcomes, and heart rate is a risk factor for cardiovascular events in this condition. SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine Trial) enrolled 6505 chronic heart failure patients in sinus rhythm with a recent heart failure hospitalization, low EF ≤35%, and elevated heart rate ≥70 bpm to investigate the role of heart rate in heart failure. Patients were randomized to either the specific heart rate–reducing agent ivabradine, an If current inhibitor, or to placebo, on top of the best possible recommended heart failure therapy. The addition of ivabradine resulted in a highly significant 18% reduction in the occurrence of the primary composite end point, cardiovascular mortality or heart failure hospitalization. This beneficial effect was mainly driven by significant 26% reductions in heart failure deaths and heart failure hospitalizations. Overall, the safety of ivabradine was good; in particular, the number of bradycardic adverse effects was low. This good cardiac tolerability was recently confirmed in a 24-hour Holter monitoring sub-study. Ivabradine also improved quality of life. In patients with reduced EF, elevated heart rate, and in sinus rhythm, the addition of ivabradine on top of recommended heart failure medications improves cardiovascular outcomes. Special attention should be paid to heart rate measured under standardized conditions, and efforts should be made to reduce elevated heart rate to <60 bpm.

Medicographia. 2011;33:389-393 (see French abstract on page 393)
failure treatment with the $I_f$ inhibitor ivabradine Trial) whether specific heart rate reduction obtained by a heart rate–reducing agent devoid of any other significant pharmacological properties, the $I_f$ channel inhibitor ivabradine, would be beneficial in this condition. This question is all the more important as recent surveys conducted in Europe suggest that more than 50% of patients with heart failure have an elevated heart rate, suggesting therefore that underdosage is common in real life.10,11

Major findings from SHIFT

In a population of 6505 chronic heart failure patients with reduced ejection fraction, who had experienced a recent heart failure hospitalization, were in sinus rhythm, and with elevated heart rate $\geq$70 bpm, the addition of ivabradine 5 mg to 7.5 mg bid on top of the best possible recommended therapy provided additional benefit and significantly reduced the occurrence of the primary composite outcome, cardiovascular mortality or heart failure hospitalizations, by 18%. This effect is driven mainly by a significant reduction in heart failure hospitalizations (-26%) and heart failure deaths (-26%) (Figure 1).12

This beneficial effect was observed in a well-treated population: 93% of the patients were taking an angiotensin-converting enzyme inhibitor and/or an angiotensin receptor blocker, and 89% were receiving a $\beta$-blocker. Moreover, 56% of these patients were receiving at least 50% of the $\beta$-blocker target dose recommended by the European Society of Cardiology guidelines and 26% were at target dose.

The baseline characteristics of the population show that this was a relatively young, predominantly male (76%) population with a mean age of 60 years and with ischemic etiology (68%). The mean ejection fraction was markedly diminished (29%), and patients were almost evenly distributed in terms of heart failure severity, based on NYHA (New York Heart Association) class (49% in class II, 51% in class III/IV).

**Figure 1.** Kaplan-Meier cumulative event curves for different end points in SHIFT.
Primary composite outcome (Panel A); cardiovascular mortality or heart failure hospitalization and its two components cardiovascular mortality (Panel B); heart failure hospitalizations (Panel C) and heart failure deaths (Panel D) in the ivabradine and the placebo arms of SHIFT.

**Abbreviations:** CV, cardiovascular; HF, heart failure; SHIFT, Systolic Heart failure treatment with the $I_f$ inhibitor Ivabradine Trial.

Selected abbreviations and acronyms

- CIBIS-ELD: Cardiac Insufficiency Bisoprolol Study in Elderly
- NYHA: New York Heart Association
- SHIFT: Systolic Heart failure treatment with the $I_f$ inhibitor Ivabradine Trial
The beneficial effect on the outcomes detailed above occurred rapidly, and the survival curves show that the separation was rapid after randomization. This mirrored heart rate reduction, which occurred early on; heart rate decreased from 80 to 64 bpm 1 month after randomization in the ivabradine group, and the difference, corrected for placebo, was 11 bpm. The difference in heart rate between the two groups was 8 bpm at the end of the trial.

The reduction in the occurrence of the primary composite end point was consistent in all prespecified subgroups, including age, sex, etiology of heart failure, and use/nonuse of β-blockers, with one notable exception: the magnitude of benefit derived from ivabradine was significantly greater in the subgroup with baseline heart rate above the median value (77 bpm in the SHIFT population).

In the subgroup of patients receiving at least 50% of the target dose of β-blockers, the effects of ivabradine were consistent with those observed in the overall population, although less marked, probably due to a lower rate of cardiovascular events and therefore a limited power.

This excellent cardiac tolerability was recently confirmed by a 24-hour Holter substudy conducted in 602 patients: in the 501 patients suitable for analysis after 8 months of treatment, the number of pauses was similar in both groups; while in the ivabradine group the number of second or higher degree atrioventricular blocks was smaller (4 vs 9); there were no cases of third degree AV block; and only the number of heart rate episodes <40 bpm increased (54 vs 21).

### Clinical implications

The first lesson from SHIFT is therefore that the addition of the selective heart rate–reducing agent ivabradine on top of the best possible recommended therapy, including β-blockers in 90% of cases, significantly improves cardiovascular outcomes and particularly hospitalizations or deaths related to heart failure, with good tolerability.

SHIFT suggests therefore that greater attention should be paid to a simple biomarker, resting heart rate, a powerful predictor of outcomes in chronic heart failure. Indeed, epidemiological studies suggest that despite the dissemination of β-blocker therapy, heart rate remains elevated >70 bpm in a substantial proportion of patients. This is at least partially the result of underdosage of this therapy as a result of poor tolerance, prescribers’ reluctance, or lack of awareness of recommended target doses in real life. In the Heart Failure pilot study, comprising 3226 patients with chronic heart failure enrolled in twelve European countries, only 21% to 37% of patients were at β-blocker target dose (of carvedilol, bisoprolol or metoprolol). In CIBIS-ELD (Cardiac Insufficiency Bisoprolol Study in Elderly), the primary objective of reaching and maintaining target dose of carvedilol or bisoprolol was observed in only 25% of patients.

### Table I. Adverse events leading to treatment discontinuation in the ivabradine and in the placebo arms of SHIFT.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Ivabradine</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events</td>
<td>14% (467)</td>
<td>13% (416)</td>
<td>0.051</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2% (70)</td>
<td>3% (82)</td>
<td>0.367</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>1% (20)</td>
<td>&lt;1% (5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>1% (28)</td>
<td>&lt;1% (5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4% (135)</td>
<td>3% (113)</td>
<td>0.137</td>
</tr>
<tr>
<td>Phosphenes</td>
<td>&lt;1% (7)</td>
<td>&lt;1% (3)</td>
<td>0.224</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>&lt;1% (1)</td>
<td>&lt;1% (1)</td>
<td>1.000</td>
</tr>
</tbody>
</table>


There was also a small but significant improvement in quality of life, assessed by change in NYHA class and patient and physician reported assessment at the last visit, in ivabradine-treated patients. This was recently confirmed by a subanalysis of health-related quality of life using the Kansas City Cardiomyopathy questionnaire, a self-reported instrument that includes several dimensions, such as symptoms, quality of life, and social limitations.

Overall, the tolerability of ivabradine was good and serious adverse effects were less frequent in the active arm than in the placebo arm (Table I). Symptomatic and asymptomatic bradycardia were reported in 5% and 6% of patients, respectively, in the ivabradine arm, but led to treatment discontinuation in only 1% of cases for each of these two adverse effects. Visual side effects were also uncommon and led to treatment discontinuation in only a few cases. Overall, approximately 70% of the patients in the ivabradine arm were at target dose (7.5 mg bid) and less than 10% had to be down-titrated to the lowest dosage (2.5 mg bid).
What should the optimal heart rate in chronic heart failure be?
Since the analysis of the relationship between heart rate reduction achieved at 28 days with ivabradine and subsequent outcomes suggests that patients with the lowest risk reached a heart rate <60 bpm, it is reasonable to recommend this target in daily practice when tolerated. There is no information available on the potential benefit/harm of lowering heart rate further, although it should be remembered that cardiac output is the product of heart rate and stroke volume, so that very low heart rates result in a significant decrease in cardiac output and therefore in reduced oxygen delivery to the body. Empirically, achieving a target heart rate at rest of 50-60 bpm therefore seems a reasonable objective.

Is uptitrating β-blockers or combining ivabradine with low/medium doses of β-blockers the best strategy?
There is no clear answer yet to this important practical question from the SHIFT results, since more than 50% of the patients enrolled in this trial were taking at least half of the target recommended dose and 26% were at target dose. The investigators were repeatedly encouraged by the Executive Committee to provide the best possible therapy to their patients, including β-blockers at target dose. The SHIFT results should therefore be interpreted as heart rate reduction by ivabradine bringing an incremental benefit in patients with elevated heart rate who are unlikely to tolerate maximal doses of β-blockers, as frequently observed in daily practice.

Can ivabradine replace β-blocker therapy in chronic heart failure?
SHIFT provides no insights into this question, since the overwhelming majority of patients included in this trial were on β-blocker therapy (90%). It was not a trial designed to compare ivabradine face to face with β-blocker therapy, and the only scientifically valid conclusion that can be drawn from SHIFT is that in chronic heart failure patients treated with β-blockers whose heart rate remains elevated for any reason, ivabradine should be considered on top of their existing therapy in order to improve outcomes, particularly heart failure events, regardless of efforts to maximize β-blocker dose. This course of action has indeed been proposed in the recently published Australian and New Zealand Guidelines. However, the magnitude of the benefit provided by ivabradine was similar in the small subgroup who did not receive a β-blocker (10% of the population) to that observed in the rest of the population, suggesting that reducing heart rate with ivabradine in chronic heart failure patients intolerant to β-blockers provides a similar benefit to that observed in other patients and could be considered as an alternative.

Can the results be generalized to the overall heart failure population?
Patients in SHIFT were selected on the basis of several criteria: high resting heart rate >70 bpm, normal heart beat (sinus rhythm), and reduced ejection fraction (≤35%). In addition, the proportion of elderly patients was limited. Therefore, the effects of ivabradine cannot be generalized to apply in the overall heart failure population, nor in particular to patients with permanent atrial fibrillation (where there is no indication for ivabradine due to the mechanism of action of this drug) or to patients with heart failure and preserved ejection fraction.

Conclusion
SHIFT has brought new insights into the role of heart rate as a risk factor in chronic heart failure and on the importance of heart rate reduction—when elevated—in improving outcomes in heart failure in sinus rhythm and with reduced ejection fraction. The addition of a specific bradycardic agent, ivabradine, to the best possible recommended heart failure therapy provides a significant improvement in cardiovascular outcomes in this population and should be considered to further reduce the burden of chronic heart failure and the risks related to this disorder. The tolerability of the combination of this new heart rate–reducing agent with β-blockers was good, particularly with regards to cardiac safety.

References
Keywords: chronic heart failure, heart rate, clinical trial, heart rate reduction
Heart rate in heart failure: a novel cardiovascular risk factor

by J. S. Borer and W. Khan, USA

Heart rate (HR), a simple and easily measured clinical parameter, is now known to hold a substantial amount of independent prognostic information in the free-living population as a whole, and in a number of subpopulations with various forms of heart disease. The latter include those with coronary artery disease (CAD), hypertension, and chronic heart failure (HF) (Figure 1). Much of the supporting information is derived from epidemiological studies and, thus, suggests that HR is a risk factor for these conditions, but in the absence of prospective demonstration from randomized clinical trials, cannot definitively establish HR as a risk factor. Nonetheless, this association is biologically plausible: experimentally, HR has been shown to be directly related to the progression of coronary atherosclerosis; clinically, HR is directly related to the likelihood of disrupting preexisting atherosclerotic plaque. Most recently, in a large placebo-controlled clinical trial, HR was found to be directly associated with outcome among patients with HF. The latter association also has biological plausibility: failing myocardium has a negative force-frequency association and is energetically starved. HR reduction can improve contractility, perhaps by reducing energy expenditure, decreasing myocardial oxygen consumption, and enhancing the relationship between energy requirements and...
energy availability. Therefore, it is possible that HR-slowing therapies may hold a particular advantage for patients with various forms of cardiovascular disease (CVD). Indeed, guidelines from the European Society of Cardiology and European Society of Hypertension already recommend recognition of HR as a cardiovascular risk factor. This review article aims to assess the accumulating evidence in support of HR as a risk factor for cardiovascular mortality and morbidity, specifically in HF.

Heart rate and mortality in different populations

Unselected populations
Beginning as early as 1945, many epidemiological studies have reported that HR is strongly and directly associated with all-cause and cardiovascular mortality in unselected (“nondiseased”) populations. For example, in a Framingham cohort of 5070 subjects free from clinically apparent CVD at study entry, cardiovascular and noncardiovascular mortality increased progressively with resting HR, irrespective of age. Similarly, in three studies organized in Chicago, all in males, HR at rest was directly associated with sudden cardiac death. More recently, two large prospective studies have confirmed the strong and graded relationship between resting HR and cardiovascular and total mortality. In the Paris Prospective Study of >5000 men aged 42 to 53 years, HR was measured at rest every year for 5 consecutive years. Those participants whose HR decreased during the 5 years had a 14% (P=0.05) decrease in mortality risk compared with those whose HR was unchanged; men with increased HR during the 5 years had a 19% (P<0.012) increase in mortality. Among 21 853 men and women in the prospective national FINRISK study (Finland Cardiovascular Risk Study), a strong, graded, independent relationship between resting HR and incident CVD was also demonstrated. A resting HR of more than 90 beats per minute (bpm) was associated with an almost twofold increase in cardiovascular mortality rate in men and a threefold increase in women, compared with a resting HR of less than 60 bpm. These results confirmed findings from other studies indicating the independence of HR effect from sex. Finally, in a prospective study of Chinese adults followed on average for 8.3 years, HRs of 75-89 bpm and ≥90 bpm in men resulted in a 1.23-fold increase in the risk of CVD, respectively, compared with lower HR. Similarly, in women, there was a 1.23-fold increase in risk if HR exceeded 90 bpm. A unique finding in this study was increased stroke risk in subjects with HR ≥90 bpm, not found in Western populations.

Hypertension
HR varies directly with sympathetic activity and therefore could be directly related to the proclivity for hypertension. This may be one explanation for the observation that, in subjects with hypertension, cardiovascular mortality risk increases directly with HR (Figure 2). One of the strongest relationships in hypertensive patients was found by Benetos et al, who studied more than 12 000 French men aged 40 to 69 years. During 20 years of follow-up, the investigators found that HR was directly related to cardiovascular death, with hazard ratios of 1.35 (95% confidence interval [CI], 1.01-1.80) for HR of 60 to 80 bpm, 1.44 (95% CI, 1.04-2.00) for HR of 81 to 100 bpm, and 2.18 (95% CI, 1.37-3.47) for HR >100 bpm, compared with HR <60 bpm. In the Systolic Hypertension in Heart Failure Today: A Paradigm Shift (SHYFT) study, a reduction in HR was associated with a significant reduction in cardiovascular risk. These findings support the concept that HR is an independent predictor of cardiovascular mortality in hypertensive patients.
in Europe (Syst-Eur) trial, clinic and ambulatory HR was directly associated with all-cause, cardiovascular, and noncardiovascular mortality among both elderly hypertensive men and women. In addition to the association between initial study HR and outcome, HR while on treatment in hypertensive patients also predicts likelihood of subsequent cardiovascular events.24 In a study of 9190 hypertensive patients with echocardiogram-indicated left ventricular hypertrophy followed for almost 5 years while being treated with losartan-based or atenolol-based regimens, HR increments of 10 bpm while on treatment were associated with a 25% increment in cardiovascular death and a 27% increment in all-cause mortality. In an alternative analysis, persistence or development of HR ≥84 bpm (upper quintile of baseline HR) was associated with an 89% greater risk of cardiovascular death and a 97% increased risk of all-cause mortality compared with lower HR. These findings support the value of serial assessment of HR for risk stratification in hypertensive patients.

The relationship between resting HR and adverse outcomes in patients with hypertension and CAD was examined in INVEST (INternational VErapamil-SR/trandolapril STudy).4 In this study of 22,576 hypertensive patients with CAD randomized to either verapamil SR-based or atenolol-based treatment strategies, baseline HR was directly associated with adverse outcomes, which were twofold greater among patients with HR >100 bpm than among those with HR <100 bpm. A linear relationship was observed between baseline HR and risk of adverse outcomes: 5-bpm increments were associated with 6% risk increments.

**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ARIC</td>
<td>Atherosclerosis Risk In Communities (study)</td>
</tr>
<tr>
<td>BEAUTIFUL</td>
<td>morBidity-mortality EvAluaTion of the</td>
</tr>
<tr>
<td>BPM</td>
<td>beats per minute</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CASS</td>
<td>Coronary Artery Surgery Study</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>DPP</td>
<td>Diabetes Prevention Program</td>
</tr>
<tr>
<td>FINRISK</td>
<td>Finland Cardiovascular Risk Study</td>
</tr>
<tr>
<td>GISSI</td>
<td>Gruppo Italiano per lo Studio della Streptochinasi nell’infarto miocardico</td>
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<tr>
<td>HF</td>
<td>heart failure</td>
</tr>
<tr>
<td>HR</td>
<td>heart rate</td>
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<tr>
<td>INVEST</td>
<td>INternational VErapamil-SR/trandolapril STudy</td>
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<td>SHIFT</td>
<td>Systolic Heart failure treatment with the</td>
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<tr>
<td>STEMI</td>
<td>ST-segment elevation myocardial infarction</td>
</tr>
<tr>
<td>Syst-Eur</td>
<td>Systolic Hypertension in Europe (trial)</td>
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<tr>
<td>TNT</td>
<td>Treating to New Targets (trial)</td>
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**Diabetes**

Impaired autonomic function is associated with abnormal concentrations of serum insulin and abnormal insulin resistance, independent of blood glucose concentrations. This suggests that autonomic dysfunction may be a consequence and also a precursor to hyperglycemia. The relationship between autonomic dysfunction and development of diabetes was further explored in the ARIC study (Atherosclerosis Risk In Communities). The authors demonstrated that individuals with autonomic dysfunction, determined by low HR variability and high resting HR, were at a relatively high risk of developing diabetes over the succeeding 9 years, even when body mass index and physical activity were taken into account. Furthermore, in a post hoc analysis of the Diabetes Prevention Program (DPP) randomized trial of more than 3000 nondiabetics with abnormal fasting and postload plasma glucose concentrations, who were assigned to placebo, metformin, or a lifestyle-modification program, lower HR was associated with lower risk of developing diabetes, independent of weight change.

HR is also a powerful predictor of cardiovascular outcomes in established diabetics. This was clearly demonstrated in a study of 475 patients (aged 55 to 75 years) with type 2 diabetes who were followed over the course of 5 years, during which 57 (13.5%) died due to cardiovascular causes. In this population, HR >75 bpm was associated with an odds ratio for cardiovascular death of 3.3 (95% CI, 1.33-8.19) compared with the risk at lower HR. In another study of 14,992 Medicare participants aged 35 to 64 years who were free from diabetes at baseline (1992), over the next 10 years, HR was associated with diabetes mortality in those aged 35 to 49 years at baseline when adjustment was made for postload glucose and body mass index.

**Coronary artery disease**

Experimental data suggest that tachycardia results in development and progression of atherosclerosis. Reasons may include the direct relation of HR to hemodynamic shear stress (possibly due to shortening of diastole and changes in flow direction), which may damage intercellular junctions, increasing the permeability of endothelial cells and facilitating the ingress of atherogenic particles into the intima media.30 Tachycardia also tends to increase mean arterial pressure by shortening diastole, thus increasing pulse pressure. The result is an increase in cardiac workload and thickening of arteriolar smooth muscle.31 HR is also inversely related to arterial compliance.32 Studies in experimental animals support the relationship between HR and CAD. Beer et al ablated the sinus node in adult monkeys and also studied an equal number of nonablated monkeys, all fed on an atherogenic diet for 6 months. The controls, with persistently higher HR, had a significantly higher number of and more serious coronary artery atherosclerotic lesions than the test animals (P<0.02). Similar relationships have been reported in other studies.
A direct relationship between HR and progression of coronary atherosclerosis has also been shown in humans. Perski et al observed that HR on 24-hour ambulatory electrocardiogram predicted progression of CAD, independently of (and, indeed, more predictively than) conventional risk factors. Huikuri et al described the association between HR and progression of focal coronary atherosclerosis in patients with coronary artery bypass grafts.

The prognostic importance of HR in patients with known chronic CAD and in those surviving after myocardial infarction has been repeatedly demonstrated. In a large cohort of Israeli patients hospitalized for acute myocardial infarction in 1985-1986, Disegni et al recorded all deaths during initial hospitalization and at 1 year post discharge. On multivariate analysis, admission HR was an independent predictor of in-hospital and 1-year postdischarge mortality. The CASS (Coronary Artery Surgery Study) registry investigated the long-term prognostic value of resting HR in nearly 25 000 patients with suspected or proven CAD. Cardiovascular mortality increased progressively with increasing HR: resting HR >83 bpm was a strong predictor of overall mortality (hazard ratio, 1.32; 95% CI, 1.19-1.47; P<0.0001) and cardiovascular mortality (hazard ratio, 1.31; 95% CI, 1.15-1.48; P<0.0001), independent of known risk markers such as hypertension, diabetes, smoking, left ventricular ejection fraction, and the number of hemodynamically significantly diseased coronary vessels. In INVEST, in patients with hypertension and CAD, baseline and follow-up resting HR were directly associated with risk of adverse outcomes. Hjalmarson et al demonstrated that admission HR in patients with myocardial infarction is directly related to clinical outcome: they reported all-cause mortality at 1 year of 14% when admission HR was <60 bpm, 41% when admission HR was >90 bpm, and 48% when admission HR was >110 bpm. Meta-analyses of the GISSI-2 and GISSI-3 trials (Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto miocardico), which included about 20 000 patients, found that in-hospital mortality rates after myocardial infarction rose from 3.3% for patients with admission HR <60 bpm to 10.1% for patients with admission HR >100 bpm. As a corollary, both mean HR and failure of HR to fall between hospital days 1 and 7 carry a poor prognosis. HR is also an independent prognosticator in patients with acute ST-segment-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention. An analysis of 6-month follow-up data from 2477 consecutive patients with STEMI treated by primary percutaneous coronary intervention revealed that HR >80 bpm was associated with more than a twofold increased risk of death compared with lower HR.

The value of HR as a prognostic factor was also evaluated in the 5438 patients in the placebo arm of BEAUTIFUL (morbidity-mortality EvaLUaTion of the Iβ inhibitor ivabradine in patients with coronary artery disease and left ventricular dysfunction). This large cohort with stable CAD and left ventricular dysfunction was divided into those with HR ≥70 bpm and those with HR <70 bpm at study entry. The group with higher entry HR had significantly higher adverse cardiovascular outcome rates compared with those who entered with lower HR (34% greater cardiovascular death, and higher hospital admissions for HF; myocardial infarction, and revascularization [53%, 46%, and 38%, respectively]). These findings have recently been corroborated by results from the TNT trial (Treating to New Targets). An analysis of 9580 subjects followed for a median of 4.9 years revealed a major cardiovascular event rate of 11.9% in those with a baseline HR of ≥70 bpm compared with a rate of 8.8% in those with a baseline HR <70 bpm.

**Congestive heart failure**

The prognostic value of resting HR extends to patients with chronic HF. HF is common, disabling, and serious, affecting roughly 2% to 3% of the population in developed countries. Standard pharmacological treatment for HF includes β-blockers and renin-angiotensin-aldosterone system antagonists. β-Blockers, a mainstay of therapy, are associated with reduced morbidity and mortality beyond that achieved with renin-angiotensin-aldosterone system antagonists. These benefits seem to be linked, at least in part, to their HR-lowering properties. HR reduction in these studies was fairly similar, and the results suggested that mortality benefits were directly related to magnitude of HR reduction. However, these studies could not separate the effects of HR reduction from those of other potentially important actions of β-blockers, such as antiarrhythmic effects, inhibition of maladaptive β-adrenergic signaling pathways producing apoptosis, or reduction of β-adrenergic signaling dysregulating contractility.

**The impact of SHIFT**

In recent decades, the association between HR and cardiovascular morbidity and mortality in HF has been increasingly appreciated, but the impact of HR modulation has remained less than totally clear because of the relationship between HR and conventional CVD risk factors. Thus, it has been unclear as to whether HR is a marker of underlying hemodynamic and metabolic abnormalities and therefore, of risk, or whether HR is truly an independent risk factor, downward modification of which is associated with reduction in risk. Assessment of this issue required a therapeutic modality that could reduce HR without affecting other aspects of cardiovascular function and pathophysiology. Ivabradine, as a selective HR-reducing agent (via blockade of the sinoatrial node
If current [“funny” current, mediated by voltage-dependent cyclic AMP interactions] with no other apparent cardiovascular effects), provided a unique opportunity to define the impact of pure HR reduction in HF. To address this, SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine Trial) investigated the effects of HR reduction with ivabradine on clinical outcomes in HF.\(^9\),\(^10\) SHIFT was an event-driven, randomized, double-blind, placebo-controlled trial in which either ivabradine or placebo was administered for a median of 22.9 months to 6505 patients who were also receiving a background of guideline-defined standard multidrug therapy on evidence-based recommended doses or maximally achievable dosages if lower than recommended. The primary outcome event in SHIFT was the composite of death or HF hospitalization in patients with moderate-to-severe chronic HF and left ventricular systolic dysfunction.\(^9\) The results of SHIFT were compelling; the primary outcome was 18% lower (\(P<0.0001\)) among patients receiving ivabradine than among those receiving placebo (Figure 3).\(^9\),\(^10\) The effect on the primary outcome was predominantly driven by a 26% reduction in hospital admissions for worsening chronic HF (\(P<0.0001\)) and deaths due to HF, which were also reduced by 26% (\(P=0.014\), Figure 4). There was a trend toward a reduction in cardiovascular death (hazard ratio, 0.91; \(P=0.128\)) and mortality (hazard ratio, 0.90), and fewer all-cause hospital admissions with ivabradine (hazard ratio, 0.89; \(P<0.003\)). Ivabradine was well-tolerated: health-related quality of life, assessed with the Kansas City Cardiomyopathy Questionnaire, was significantly improved with ivabradine relative to placebo, a finding not reported in any of the \(\beta\)-blocker trials. The findings were consistent across several prespecified subgroups. Among these was etiology of HF. Although the underlying cause of HF in two thirds of the study population was CAD/ischemic heart disease, one third had idiopathic cardiomyopathy as the underlying etiology. The benefits of ivabradine versus placebo were statistically indistinguishable across these etiologies. Importantly, among patients who had the highest HR at study entry and were, therefore, at greatest risk, those on ivabradine had the largest reduction in HR and outcome events relative to placebo. In a companion analysis focusing specifically on HR effects, it was demonstrated that event frequency in the placebo group was 2.9% higher with every 1-beat increase from the admission HR minimum of 70 bpm.\(^10\) The finding of this direct relationship between

**Figure 3.** Ivabradine improves outcomes in heart failure.

**Figure 4.** Ivabradine significantly reduces death from heart failure.

**Figure 5.** Data from the placebo group in SHIFT.

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**Abbreviations:** CV, cardiovascular; HF, heart failure; HR, hazard ratio; NNT, number needed to treat.

**After reference 9:** Swedberg K et al. Lancet. 2010;376:875-885. © 2010, Elsevier Ltd.

pretreatment HR and adverse outcome in the placebo group confirms the importance of HR as a risk marker (Figure 5). More importantly, the reduction in outcome events with ivabradine relative to placebo within each quintile of pretreatment HR ranges indicates that HR is, in fact, a risk factor for HF; i.e., that it not only indicates risk, but that its therapeutic downward modulation reduces risk. The results of SHIFT clearly establish that HR reduction is an important part of the management of HF.

Conclusions
To establish the clinical validity of epidemiological association between a risk factor and any CVD, several criteria should be satisfied. The risk factor must have a direct relation with the likelihood of a disease, should contribute to the development of the disease regardless of sex, age, or race, should manifest a relationship with outcome that is statistically independent of other known or previously accepted risk factors and, most importantly, when it is modified to reduce its magnitude, this modification must similarly modify the outcome (beneficially) of the disease. In addition, to be clinically useful, the risk factor must be readily measurable and there must be considerable evidence linking the risk factor to the disease.

As noted previously, many studies have shown that HR, an easily measured clinical variable, is a significant predictor of total mortality and cardiovascular mortality. This relationship is strong, graded, and independent of other prognostic factors. Confirmation from SHIFT that HR reduction reduces cardiovascular events in patients with HF clearly establishes HR as a true risk factor for this disease, as it also appears to be for CAD. Therefore, it is reasonable and appropriate to consider HR in risk stratification and as a guide for medical therapy, specifically that involving the administration of ivabradine in addition to other already established HF therapies, in patients with HF.

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La fréquence cardiaque (FC) est un paramètre facile à mesurer employé de façon universelle en évaluation clinique. Ces 65 dernières années, de nombreuses études ont établi l’utilité de la FC comme marqueur de risque d’événements cardio-vasculaires et de mortalité totale dans des populations non sélectionnées (< non malades >) ainsi que dans des cohortes de patients atteints de maladie coronaire, d’hypertension et d’insuffisance cardiaque. Cependant, pour établir un marqueur de risque comme facteur de risque, il faut démontrer non seulement que les résultats sont quantitativement liés au facteur, mais aussi que la modification du facteur de risque présumé modifie de la même façon l’évolution de la maladie. Il faut d’abord, pour démontrer que la FC est un facteur de risque d’insuffisance cardiaque, avoir un traitement qui modifie la FC, sans agir sur d’autres paramètres cardio-vasculaires, et ensuite appliquer le traitement aux patients atteints d’insuffisance cardiaque. L’ivabradine remplit le premier critère et l’étude SHIFT (Systolic Heart Failure treatment with the i inhibitor ivabradine Trial) a démontré qu’elle était nettement supérieure au placebo pour améliorer les résultats cardio-vasculaires quand elle est administrée dans un contexte de traitement pharmacologique standard basé sur des recommandations pour l’insuffisance cardiaque. En conclusion, selon SHIFT, la FC devrait désormais être considérée comme facteur de risque d’insuffisance cardiaque, et la modulation de la FC, en particulier avec l’ivabradine, devrait être prise en compte dans la prise en charge des patients atteints d’insuffisance cardiaque systolique modérée à sévère.

Keywords: cardiovascular disease; coronary artery disease; heart failure; heart rate; ivabradine; risk factor; risk marker
Heart failure (HF) is a major challenge for health care systems. In acute HF, the main aim of clinical management is to stabilize the clinical condition, clarify the etiology and precipitating factors, and provide quick symptom relief. In both acute and chronic HF, it is advisable to use a multi-marker approach, factoring in several diagnostic and therapeutic pathways simultaneously. The pharmacological approach recommended by current guidelines is a step-by-step procedure. Angiotensin-converting enzyme inhibitors and diuretics are the mainstay of therapy. The next step is β-blockers, which should be uptitrated to the maximum dosage possible. This therapeutic strategy is supported by several large-scale trials, which have shown a significant improvement in survival. Most patients, however, cannot tolerate maximum β-blockade and for these, ivabradine is a life-saving therapeutic option, to be used either in combination with β-blockers or alone in patients with comorbidities. Once these therapies have been implemented, aldosterone antagonists, angiotensin II receptor blockers, metabolic therapy, and iron therapy can all be considered. Furthermore, resynchronization therapy and cardioverter defibrillators should be implanted in all eligible patients. In spite of these clear guidelines, most patients with HF continue to receive suboptimal care, and most of them remain moderately or severely symptomatic. Multidisciplinary management programs have been developed to promote further improvement and implementation of appropriate HF management. Close monitoring of patients during the entire course of the disease encourages self-care management and, consequently, adherence to medication and diet, ensures better symptom recognition, and thus has a considerable impact on symptoms, well-being, and prognosis.

Heart failure (HF) is a common disease that is increasingly recognized as a major health burden, with a dramatic impact in terms of consumption of human and economic resources, and is one of the major challenges for health care systems throughout the world. The worldwide prevalence of HF is 2% to 2.5%; it affects close to 6 million people in the US and 14 million people in Europe. HF is the first cause of morbidity and mortality due to cardiovascular disease and results in more hospitalizations than all forms of cancer combined. HF remains disabling even after discharge from the hospital, as it considerably impairs quality of life and constitutes a risk factor for stroke, renal failure, and early readmission.
HF prevalence increases with age, from 1% to 2% in individuals aged 45 to 54 years to >10% in those aged ≥75 years. Approximately 80% of patients hospitalized due to HF are older than 65 years. With a population that continues to age and (paradoxically) with the continuing improvement in the treatment of hypertension and myocardial infarction, HF is the fastest-growing clinical cardiac disease entity in all countries and its management is therefore assuming pivotal importance.

HF is often caused by ischemic cardiomyopathy, but may also occur in the presence of normal or nearly normal cardiac function. Its clinical presenting signs include shortness of breath and fatigue (left ventricular failure) or physical signs of fluid retention (right ventricular failure).

Management of heart failure
The current guidelines of the European Society of Cardiology for the diagnosis and treatment of HF call for a quick and efficient approach. This is especially true for acute HF, in the context of urgent, unplanned hospitalization. In this case, HF management begins in the Emergency Department, continues during hospitalization, and extends after discharge. In the Emergency Department, the management of acute HF aims to stabilize the patient’s clinical condition, clarify the etiology and the precipitating factors, and initiate treatment to provide quick symptom relief. Respiratory support with use of oxygen if necessary, and noninvasive positive pressure ventilation should be provided, in order to avoid intubation. Admissions for worsening HF represent a significant health care burden and lead to significant impairment of patient quality of life; they are associated with increased short-term and long-term mortality. This is why special emphasis should be laid on ensuring the best possible management of chronic HF, in order to reduce the need for (re)hospitalization and improve prognosis.

According to current guidelines, the first step in HF management is taking a comprehensive history and carrying out a thorough physical examination in search of causal factors such as the presence of prior or current evidence of myocardial infarction, valvular disease, or congenital heart disease. In addition to history and physical examination, imaging techniques such as chest x-ray and echocardiography of the cardiac chambers or great vessels are used to identify causal structural abnormalities. Transesophageal echocardiography, stress echocardiography (exercise or dobutamine echocardiography), cardiac magnetic resonance imaging, cardiac computed tomography, or radionuclide imaging should be used only if the nature of HF is unclear. Coronary arteriography should be performed in HF patients with angina or significant ischemia unless the patient is not eligible for revascularization. Pulmonary function tests may be useful in assessing potential respiratory causes of dyspnea.

Evaluation of dyspnea and fatigue, as well as exercise capacity and exertional symptoms relies on exercise testing (determination of mixed venous oxygen saturation [MVO₂] or 6-minute walk test [6MVWT]). Physical training improves symptoms and quality of life in patients with chronic HF and is associated with positive effects on morbidity and mortality.

To conclude, HF risk stratification requires a multimarker approach based on making an adequate selection of biomarkers known to be individually associated with HF, taking into account several biochemical pathways simultaneously. This allows better prediction of the incidence of HF and of the response to treatment.

Pharmacological treatment
In spite of the variety of pathophysiological causes, HF is consistently characterized by the presence of neurohumoral activation, metabolic disorders such as testosterone deficiency and insulin resistance, and a metabolic shift favoring catabolism and impairment in skeletal muscle bulk and function. Consequently, therapeutic strategies targeted to these pathophysiological processes have been developed over the last decades, which have resulted in a substantial improvement in survival rate of patients with HF.

Current guidelines recommend pharmacological treatment based on a stepped-care approach. The first step involves angiotensin-converting enzyme inhibitors (ACE inhibitors)
and diuretics. The second step calls for the introduction of β-blockers. The third step consists in uptitrating β-blocker therapy to reach the maximum dosage possible.

**ACE-inhibitors and diuretics**

ACE inhibitors are the cornerstone of treatment of patients with HF and are recommended as first-line therapy in all patients with current or prior symptoms of HF and reduced left ventricular ejection fraction (LVEF), unless contraindicated. They exert beneficial effects on cardiac and systemic hemodynamics, the neuroendocrine system, and vascular function, leading to reduction in blood pressure, preload, and afterload. ACE inhibitors also have structural effects on the myocardium, resulting in regression of left ventricular hypertrophy, reduction in interstitial collagen deposition and fibrosis, and prevention of cardiac remodeling.15

In patients with current or prior symptoms of HF and reduced LVEF who have evidence of fluid retention, diuretics and salt restriction are indicated, concurrently with ACE inhibitors. In patients with congestive HF, diuretics are of pivotal importance in the presence of symptoms and signs of volume overload. Diuretics are often the mainstay of the treatment of the elderly and patients with diastolic dysfunction, as they allow to generate low-normal to normal cardiac output in these patients who are extremely sensitive to changes in volume and preload.

**β-Blockers**

As step-two therapy, β-blockers are recommended in all stable patients with current or prior symptoms of HF and reduced left ventricular EF, unless contraindi
cated.2 CIBIS III (Cardiac Insufficiency Bisoprolol Study—III) clearly showed that β-blocker therapy should be implemented only after adequate diuretic and ACE-inhibitor therapy has been instituted.17 The study failed to show noninferiority of implementation of β-blocker-first versus ACE-inhibitor-first strategy, but showed that initiation of β-blockers before optimization of ACE inhibition was associated with increased risk of hospitalization for HF. The beneficial effects of β-blockers in patients with HF involve a number of mechanisms: (i) they slow the heart rate (increasing left ventricular filling time and reducing myocardial oxygen consumption); (ii) they modify the hemodynamic response to exercise; (iii) they lower the blood pressure. These effects combine to regress left ventricular hypertrophy and reverse ventricular remodeling. In patients with HF adequately treated with ACE inhibitors, the favorable effects of β-blockers are mediated by the heart rate-lowering effect,18 as shown by a meta-analysis of 17 randomized, placebo-controlled trials of long-term treatment with β-blockers or calcium channel blockers in patients surviving myocardial infarction (Figure 1).

The randomized controlled trials (RCTs) on β-blockers in HF have been exhaustively reviewed.1,3 One of the three β-blockers that have been proven to reduce mortality (viz, bisoprolol, carvedilol, and sustained release metoprolol succinate) should be administered whenever possible.19-22 However, although β-blockers represent the mainstay of treatment of patients with HF, these drugs are most often undertitrated for various reasons, despite the lack of real contraindications.4 Our group has recently reported that, among patients with coronary artery disease, 43% of those with HF were not on β-blocker therapy (Figure 2, page 404).23

Similarly, ACE inhibitors are often prescribed at lower dosages than those known to be clinically effective.8 Thus, β-blockers and, to a lesser extent, ACE inhibitors are often not adequately prescribed in patients with HF, most of whom remain moderately or severely symptomatic, because treatment is suboptimal.24 The major problem in implementing the therapeutic dosages of these drugs is hypotension due to the concomitant effect of drugs with hemodynamic action.

**Ivabradine**

In these patients, ivabradine plays a central role. This specific and selective β blocker has been found to improve ischemia-related end points, either alone or in association with β-blockers. SHIFT (Systolic Heart failure treatment with the β inhibitor ivabradine Trial) has shown a significant reduction in mortality and hospitalization for HF with ivabradine.25 The prognostic
benefit is related to the magnitude of heart rate reduction and, indeed, patients achieving an heart rate <60 beats/minute are those with the greater survival benefit. Our group has recently consistently shown that in patients receiving inadequate ACE-inhibitor dosages and in those naïve to β-blockers, ivabradine alone or in combination with carvedilol was superior to carvedilol alone in improving exercise capacity and quality of life (Figure 3).\textsuperscript{21} As aforementioned, patients with HF who are candidates for ivabradine are those without atrial fibrillation and not on β-blockers (or receiving inadequate dosages of β-blockers) because of hypotension and other side effects. In these patients, ivabradine improves symptoms, quality of life, and prognosis. Given the fact that β-blockers are so often not used at adequate dosage, their combination with ivabradine may represent an effective alternative strategy for reducing heart rate in patients with HF.\textsuperscript{25,26}

Once these therapies have been implemented, angiotensin II receptor blockers (ARBs), aldosterone antagonists, metabolic therapy, and iron therapy can be considered.

**Additional pharmacological therapies**

- **Angiotensin receptor blockers**

ARBs may have a small additional protective effect in patients with HF who are intolerant to ACE inhibitors and/or in those who remain symptomatic despite maximally uptitrated therapy with ACE inhibitors and β-blockers. Use of ARBs should be limited to these patients only, since it is preferable to achieve maximal uptitration of effective therapies such as ACE inhibitors and β-blockers in patients with HF.

ARBs are also recommended in patients with current or prior symptoms of HF and reduced LVEF who are intolerant to ACE inhibitors.\textsuperscript{9} Addition of an ARB may be considered in persistently symptomatic patients with reduced LVEF already being treated with maximally uptitrated conventional therapy.\textsuperscript{27} OPTIMAAL (OPTimal Trial In Myocardial infarction with the Angiotensin II Antagonist Losartan) failed to show noninferiority of losartan to captopril in patients with HF and acute myocardial infarction, but found that fewer patients discontinued the study medication when allocated to losartan (Figure 4).\textsuperscript{28} Thus, although ACE inhibitors should remain the first-choice treatment in HF patients, losartan can be considered in those who are intolerant to ACE inhibitors.

- **Hydralazine–isosorbide dinitrate combination**

Combination treatment with hydralazine and isosorbide dinitrate is an alternative in patients intolerant to both ACE inhibitors and ARBs. This combination should be considered in all patients with HF and persistent symptoms despite maximal treatment. It is effective in reducing the risk of death, and this is particularly true in black patients, known to have reduced sensitivity to ACE inhibitors.\textsuperscript{7} It is also useful in patients with current or prior symptoms of HF and reduced LVEF in whom ACE inhibitors and ARBs are contraindicated because of drug intolerance, hypotension, or renal insufficiency.\textsuperscript{29}

- **Aldosterone receptor blockers**

Aldosterone receptor blockers may be considered in selected patients with moderately severe to severe HF and reduced LVEF who can be carefully monitored for renal function and potassium concentration. Aldosterone receptor blockers are potentially able to improve cardiac function by blocking the effects of aldosterone and thus interfering with collagen deposition and cardiac fibrosis.\textsuperscript{30}
and atrial fibrillation, which is a frequent occurrence in older patients with current or prior symptoms of HF, reduced LVEF, and dyssynchrony. Studies have shown that the combined use of an ACE inhibitor, an ARB, and an aldosterone receptor blocker is not recommended in patients with current or prior symptoms of HF and reduced LVEF. Also, the combined use of an ACE inhibitor, an ARB, and an aldosterone receptor blocker is known to adversely affect the clinical status of patients with current or prior symptoms of HF and reduced LVEF.

**Device therapy: cardiac resynchronization and implantable cardioverter-defibrillators**

As an adjunct to optimal medical therapy, cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillators (ICD) should be used in all eligible patients. As recommended by the recent European guidelines on device therapy in HF, CRT and ICD should be used in patients with severe HF (New York Heart Association [NYHA] class III-IV) who remain symptomatic and with QRS prolongation despite optimal medical therapy. As summarized in a recent review, clinical trials have shown that HF patients implanted with a device had a remarkably low mortality rate. CRT and ICD have also been found to reduce morbidity and mortality in patients with mildly symptomatic HF (NYHA class I-II).

CRT has resulted in substantial improvement in symptoms and a large reduction in mortality by reducing both sudden death and death due to HF. In HF patients, dyssynchronous contraction can be addressed by electrically activating the right and left ventricles in a synchronized manner with a biventricular pacemaker device. Short-term use of CRT has been associated with improvement in cardiac function and hemodynamics, significant improvement in quality of life, functional class, exercise capacity, and LVEF, as well as with reduction in hospitalizations and all-cause mortality.
ICD implantation is indicated in HF patients with a history of previous cardiac arrest or documented sustained ventricular arrhythmia, to reduce the risk of recurrent events. In particular, it is indicated for the secondary prevention of death from ventricular tachyarrhythmia in patients with otherwise good clinical function and prognosis, or in those with chronic HF and low LVEF presenting with syncope of unclear origin. In conclusion, CRT, or a combination of CRT and ICD, is recommended in most HF patients.

How can management of heart failure patients be improved?
The past decades have seen major advances in the management of patients with HF thanks to an extensive body of evidence from RCTs, meta-analyses, and large observational studies, and the resulting revision of the guidelines. This has changed the natural course of this clinical syndrome and improved patient outcomes. However, implementation of optimal HF management is still limited in routine daily practice, and many patients remain symptomatic, with an adverse impact on quality of life, and frequently receive substandard care. Different reasons may explain this phenomenon.

First, patient characteristics in clinical practice may differ substantially from those in clinical trials. There appears to be a selection bias in RCTs, which results in underrepresentation of the elderly, women, minorities, patients with concomitant comorbidities, such as renal insufficiency, chronic lung disease, obesity, depression, and neurocognitive disorders, and, generally speaking, of patients in less good health. Conversely, patients who are more likely to adhere to the prescribed treatment and follow-up are overrepresented in RCTs.

Second, as aforementioned, β-blockers are underused, especially in outpatients with HF, as opposed to hospitalized patients. The EuroHeart Failure II survey showed that β-blockers were underprescribed in elderly patients in comparison with younger patients, though there is a substantial increase in the rate of prescription of recommended medications at discharge when compared with the first European Survey.

In addition, discharge planning and follow-up after hospitalization are frequently insufficient, leading to poor self-care behavior, inadequate support for the patients, and suboptimal treatment. Notably, poor compliance is a main factor of poor prognosis. Nonadherence to medication, diet, or symptom recognition is common and may be responsible for over one third of hospital readmissions. In contrast, good adherence has been shown to decrease morbidity and mortality and improve well-being.

There is thus room for further improvement and implementation of appropriate HF management. Current European guidelines recommend management programs to improve outcomes based on a multidisciplinary care approach that follows the HF patient along the course of the disease and calls on various services within the health care system.

Such multidisciplinary management care ensures structured follow-up to enhance patient education, optimization of medical treatment, psychosocial support, and access to care. Self-care management strategies are now recognized as an integral part of successful HF treatment, and promise to exert a significant impact on the symptoms, functional capacity, well-being, morbidity, and prognosis of heart failure patients.

References
Keywords: angiotensin-converting enzyme inhibitor; β-blocker; cardioverter-defibrillator; compliance; diuretic; heart failure; ivabradine; management; resynchronization therapy; self-care
PRISE EN CHARGE AU QUOTIDIEN DES PATIENTS INSUFFISANTS CARDIAQUES

Education of patients has improved greatly in the last few decades, but it is unclear whether motivation to act on education has. This has proved difficult to measure. Patients have a surprising number of ways of misunderstanding advice and should be encouraged to discuss any concerns. Implementation is best assessed by audit. It is also good practice to evaluate what patients have understood. Standard questionnaires have been developed to assess patients’ educational attainment about heart failure management.”

Rationale for patient education

If patients all had a personal nurse or physician to supervise them throughout each and every day then patient education would be unnecessary. Clearly this is not the case and, using conventional methods of delivering care, never can be for the vast majority of patients and interventions. In fact, one of the attractive aspects of implantable defibrillators, cardiac resynchronization, and potentially other devices for treating patients with heart failure is that once they have been successfully implanted the treatment is beyond the patients’ control. Implanted devices work 24 hours a day, 7 days per week, but can be largely forgotten by the patient. Indeed, it is probably good if patients do mostly forget that they have had a device implanted as this indicates good psychological adjustment and a lack of anxiety. However, for many aspects of heart failure management, patients need to be active participants in managing their disease to improve their quality of life, reduce the risk of hospitalization and to increase longevity. Clearly, if the medicine stays in the bottle it can’t do any good; even compliance with placebo is associated with improved outcomes—probably because it indicates that patients are taking their other medications and paying more attention to advice on lifestyle.

In order for changes in diet, exercise, and pharmacological therapy to deliver benefits, patients have to know what they should do, be willing to do it, and then take action on their intentions. Appropriate advice and effective communication is required for the first task. The patient has to be persuaded that the advice is good and
that any inconvenience, discomfort, loss of pleasure or perceived side effects are worth the potential gain. This implies either that patients know what is at stake, the size and nature of the expected benefit, and the rate and severity of potential risks, or that they trust the advice they receive and don’t question it. Clearly this is complex even for those who feel well, have full cognitive function, and are motivated, educated, and intelligent. Patients may receive advice, but remain skeptical about it. Alternatively, patients may make a choice not to give up “bad” habits, such as cigarettes or excess alcohol, in order to live a little longer, but prefer to live the remainder of their life as they wish. Health professionals are there to offer advice and support, but should not apply excessive coercion if the patient doesn’t want to take the advice proffered. If the patients do decide to follow advice, then they must have a plan to implement what they intend to do. There are many distractions, and daily routines are easily disrupted or forgotten. It is to the immense credit of patients, and those who care for them, that so many patients regularly take their medication. The extent to which they are aware of and comply with lifestyle advice is less clear. Once patients become knowledgeable and confident about the management of their heart failure, the sense of mastery may contribute to greater well-being and better outcomes.

### The educational strategy

The most important aspects of education are timing, hierarchy, content, repetition, consistency, motivation, implementation, and, finally, audit.

Timing is critical. It is important that patients are given a basic understanding as soon as possible that there is a problem with the heart and that the consequences of this can be reduced or prevented by adhering to advice and therapy. However, it is important that patients receive information at a rate they can absorb and cope with. This will vary considerably among patients. Too much education too quickly can be a bad thing. Denial of disease is an important coping mechanism for many patients. Ill-judged attempts at getting patients to understand the enormity of their problems can cause depression and despair. Unless the health professional has the skills (most don’t) to deal with the consequences of full disclosure, then considerable caution is appropriate when informing patients with heart failure about their prognosis.

However, not making patients aware of the gravity of their disease can have serious consequences if it leads them to decrease to stop treatment because of a minor side effect or not to follow advice on changes in lifestyle.

There should be a hierarchy of information with three important considerations in mind. The first consideration is context. Patients who have had a recent episode of worsening heart failure because they forgot their diuretics first need advice about diuretic compliance and investigation of the reasons for noncompliance, which might include lack of planning leading to them running out of tablets, denial of disease, cognitive dysfunction, or avoidance because of the social inconvenience of diuresis. The second consideration is about the size of impact the intervention will have on medical aspects of disease. In this sense, advice about angiotensin-converting enzyme (ACE) inhibitors and β-blockers, which have proven, substantial, and consistent benefits on symptoms and prognosis, is much more important than information about dietary sodium, adjustment of which has not been shown to be of benefit and could even be harmful, and exercise, which may improve psychological outlook, but has little or no effect in reducing either hospitalization or death. The third consideration is the patients’ mastery of their disease, in other words being confident in knowing what to do. Building confidence can mean supporting patients in doing things that they believe to be beneficial, as long as they are not harmful, in order to give a greater sense of control over their own life. This might include eating a well-balanced diet and regular exercise, neither of which is really known to have any direct benefit on the rate of hospitalization or longevity in patients with heart failure. In this sense, advice on diet and exercise may be as important as taking medication. Patients should not only be told which of their medications are known to be effective, but also those where doubt and controversy exist as they may wish to rationalize their regimen. The doctor or nurse can then add their personal opinion, but then leave the final decision with the patient.

The content is vital and should be based on professional guidelines adapted for patients’ needs. For most patients education will be delivered by a variety of media. An initial dialogue with a health professional, reinforced periodically, is the expected contemporary standard of care. However, patients often get confused by the volume of information, and therefore reinforcement with paper and electronic educational as well as practical aids such as weekly pill dispensers may make valuable additions to conventional care. The huge advantage of paper and electronic media is that patients can access it as often as they wish and discuss it with friends and family providing that vital component of education: repetition.

Paper and electronic media should also ensure consistency that should be reinforced by advice from health professionals. Patient information material and health professionals should be consistent in making clear what is evidence and what is opinion. There is no doubt that most patients with heart failure and a low left ventricular ejection fraction should receive an ACE inhibitor, a β-blocker, and an aldosterone antagonist. These are facts, not opinions, and the patient should receive a consistent message. On the other hand, there is no evidence that aspirin or statins are beneficial in patients with heart failure and coronary disease, but there are widely held opinions that such patients should take these medications. Thus, patients should be advised that aspirin and statins have not been shown to be effective and that the balance of...
harm and benefit is uncertain. Health professionals may then give their opinion on the balance of evidence without introducing dogma. If patients know what is fact and what is opinion then they are less likely to be confused by conflicting advice and can decide which advice to follow.

Ensuring that patients not only know what to do, but are motivated to do it is critical. Education of patients has improved greatly in the last few decades, but it is unclear whether motivation to act on education has. This has proved difficult to measure. Patients have a surprising number of ways of misunderstanding advice and should be encouraged to discuss any concerns. Implementation is best assessed by audit. It is also good practice to evaluate what patients have understood. Standard questionnaires have been developed to assess patients’ educational attainment about heart failure management.\(^\text{18}\) It should be routine at each clinic visit to go through a patient’s medication.

**Telemonitoring and education**

Education alone does not help patients nor will monitoring of their disease. It is the benefits of changes in mood, lifestyle, medication, and device therapy that education and monitoring help deliver that improve outcome.\(^\text{19}\) However, lack of sufficient sophistication in either education or monitoring puts the patient at risk. These activities go hand in hand and should reinforce each other. There are a relatively small number of key things, probably about ten, that a doctor or nurse needs to monitor in order to advise patients about the requirement for further intervention or adjustments to their medications (Table I). Frequent monitoring of these symptoms and signs by conventional clinical follow-up is expensive and sufficient health care resources do not exist. However, home telemonitoring is already able to do most of what is required, efficiently and cost-effectively.\(^\text{20-22}\) The last elements required, such as measurement of serum potassium, renal function, and hematocrit should soon be available. Once these are in place, the care of heart failure and many other long-term conditions will be transformed. Expert systems will be able to work with patients to monitor their condition and provide education, motivation, advice, and audit without the frequent intercession of a health-professional.\(^\text{23}\) This will start slowly at first, probably just providing advice and motivation on diet, exercise, and diuretic dosing, but within a few years this will extend to other aspects of therapy. Doubtless, these new technologies will reveal some Luddite tendencies in the profession since such systems will be perceived to usurp some of the role of doctors and nurses.\(^\text{4}\) Health professionals will still be needed to provide backup and support. Indeed, it is quite likely that telemonitoring will not reduce staffing levels, but rather

<table>
<thead>
<tr>
<th>Variable</th>
<th>Utility</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening symptoms</td>
<td>Need treatment in their own right</td>
<td>Identify and treat cause</td>
</tr>
<tr>
<td>Weight change</td>
<td>Reflects fluid balance</td>
<td>May need to adjust diuretics</td>
</tr>
<tr>
<td>Heart rate in sinus rhythm</td>
<td>Therapeutic opportunity if (\geq 70)bpm</td>
<td>Increase dose of (\beta)-blocker or add ivabradine if (\geq 70)bpm</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Therapeutic opportunity</td>
<td>Ensure on anticoagulant. Consider adding digoxin for rate control</td>
</tr>
<tr>
<td>QRS duration</td>
<td>Therapeutic opportunity</td>
<td>Consider CRT</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>Therapeutic opportunity if raised</td>
<td>(&gt;130) mm Hg suggest need for increase in (vasodilator) therapy</td>
</tr>
<tr>
<td></td>
<td>Adverse prognostic marker if low</td>
<td>(&lt;110) mm Hg indicates increased risk. Consider reducing diuretic if no fluid overload or CRT</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Anemia is a therapeutic opportunity</td>
<td>If low check for iron deficiency. More rarely, folate or vitamin B12 deficiency</td>
</tr>
<tr>
<td></td>
<td>Anemia is an adverse prognostic marker</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>Therapeutic opportunity</td>
<td>Adjust aldosterone antagonist to achieve ideal range ((4.0-5.0 \text{ mmol/L}))</td>
</tr>
<tr>
<td></td>
<td>Prognostic marker</td>
<td></td>
</tr>
<tr>
<td>Urea or creatinine</td>
<td>Renal dysfunction may exacerbate symptoms and be lethal if severe Prognostic marker</td>
<td>Adjust therapies</td>
</tr>
</tbody>
</table>

**Table I.** Key points a doctor needs to monitor in a patient with heart failure.

*Abbreviation: CRT, cardiac resynchronization therapy.*
make existing staff more effective. Think of telemonitoring as a form of radar that can be used to maintain order and to prevent or detect health crises. In fact, telemonitoring is far better used to maintain patients in a safe “envelope” using a health maintenance strategy than as a means of spotting deterioration that might lead to hospitalization requiring special intervention (a crisis detection strategy) due to the problems of false alerts. Despite some recent negative publicity based around remote monitoring using voice-interactive systems, there is compelling evidence that telemonitoring reduces mortality substantially. Telemonitoring might also reduce the rate of hospitalization, but this is less certain. Telemonitoring may increase the rate of appropriate and timely hospitalization that could be life-saving.

### Table II. Selected, larger randomized controlled heart failure trials of disease management or intervention.

<table>
<thead>
<tr>
<th>Trial</th>
<th>n=year country</th>
<th>Interventions</th>
<th>Knowledge</th>
<th>Compliance</th>
<th>QoL</th>
<th>Morbidity/ mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multifaceted Intervention26</td>
<td>2631 USA</td>
<td>Education &amp; support &amp; audit of primary care team by HF expert, Patient education materials</td>
<td>Not assessed</td>
<td>Trend to higher β-blocker use with int. (67% v 61%)</td>
<td>Not assessed</td>
<td>Not reported</td>
<td>Cluster-randomization. Atenolol, not known to be beneficial in HF, was most widely used β-blocker!</td>
</tr>
<tr>
<td>REMADHE27,28</td>
<td>350 Brazil</td>
<td>DMP with repetitive education and telephone calls</td>
<td>Not reported</td>
<td>Improved with int. P=0.0001</td>
<td>Improved with int. P=0.0001</td>
<td>Death or first hosp reduced (0.64; 0.43-0.88; P=0.008).</td>
<td>Consistent effects in subgroups. No difference in death. 0.92 (0.76 to 1.11)</td>
</tr>
<tr>
<td>Panella et al29</td>
<td>429 Italy</td>
<td>In-hospital service reorganization &amp; patient education</td>
<td>Not assessed</td>
<td>Higher use of ACE inhibitors and β-blockers</td>
<td>Not assessed</td>
<td>In-hosp mortality reduced from 15.4% to 5.6%; P=0.001. OR for mortality 0.18; 0.07 to 0.46; P=0.001 and rehosp 0.42; 0.20 to 0.87; P= 0.020</td>
<td>Cluster-randomization</td>
</tr>
<tr>
<td>COACH30-32</td>
<td>1023 Netherlands</td>
<td>FU by cardiologist vs basic or intense support by HF nurse specialist.</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>No overall effect. Trend to lower mortality with both basic and intensive support.</td>
<td>Main impact on mortality was in non-CV deaths. Patients with depression derived no benefit</td>
</tr>
<tr>
<td>HF-ACTION9,10</td>
<td>2331 USA</td>
<td>Exercise training</td>
<td>Not reported</td>
<td>Not reported</td>
<td>29% of control and 54% of int. group had &gt;5 point* change (P&lt;0.001)</td>
<td>Trends for reduction in mortality and HF hospitalization that became significant after adjustment</td>
<td>Exercise capacity improved</td>
</tr>
<tr>
<td>Galbreath33</td>
<td>1069 USA</td>
<td>Telephone nurse support</td>
<td>Not reported</td>
<td>Trend in favor of int. but poor uptake in both groups (48% vs 56%)</td>
<td>Not reported</td>
<td>Reduction in mortality (P=0.037) with trend to reduction in death or hosp. No difference in LVEF or walking distance</td>
<td>Effects greatest in patients with LVSD and more severe symptoms. Almost 50% reduction in deaths in patients tending to LVSD &amp; NYHA III</td>
</tr>
</tbody>
</table>

COACH, Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure; CV, cardiovascular; DMP, Disease management program; HF, heart failure; Int, intervention; LVSD, left ventricular systolic dysfunction. NYHA, New York Heart Association Class; QoL, quality of life; *Kansas City Cardiomyopathy questionnaire was used—a 5-point change is considered worthwhile.
**Evidence for education**

Clearly, some level of education is required for patients with heart failure to survive at all. Robust evidence that enhanced levels of education improve outcomes is lacking, but this may reflect the failure of the educational programs rather than a failure of the concept (Table II, and Table III page 414 & 415). Indeed, the major problem in studies of patient education may be the effectiveness of education in the control group that will often be higher than in usual clinical practice.

There is good evidence that patients who take treatment as advised do better, even when that treatment is a placebo. This may reflect the fact that if patients comply with placebo they also comply with other aspects of care. It is also possible that sicker patients with greater comorbidity are less likely to comply and therefore poor outcome and poor compliance are associated, but not cause and effect. Another possibility is that patients who comply are more optimistic and less depressed and that these psychological profiles are themselves associated with a better outcome. Patients rely on doctors and nurses to communicate advice effectively. However, patients are individuals and will have very different personal needs not only in terms of what they need to do and what is going to happen to them, but also how much they want to understand the reasons for the advice. Moreover, patients will differ in how they want to receive advice. Although health professionals often think they provide sufficient advice to patients, it is clear that patients often don’t recall what they have been told. For some patients, understanding the reasons for the advice will be of utmost importance, but for other patients it will be more of a burden. Ultimately, flexible, easily accessible educational systems that create a dialogue with patients, preferably linked to a telemonitoring system that can help identify the patients’ educational needs and ensure that professional support is available when needed are likely to be the most successful strategy.

**Practical implementation**

The main problems with implementing patient education are in identifying the patients, identifying their needs, and repeatedly delivering a consistent educational message with limited specialized resources. The strategy being developed in Kingston-upon-Hull is as follows (Figures 1 and 2):

- **Family physicians** are encouraged to measure plasma N-terminal pro–brain natriuretic peptide (NT-proBNP) as a routine part of the annual follow-up of patients with ischemic heart disease or diabetes mellitus and for any patient taking a loop diuretic or any other patient thought to have or be at high risk of heart failure or major cardiac dysfunction. Patients with values <200 ng/L are reassured, patients with values between 200-400 ng/L are kept under review, and patients with values >400 ng/L are referred to a heart failure specialist clinic for evaluation or, if serum creatinine is grossly elevated, to a renal clinic.
### Table III. Systematic reviews of heart failure management interventions and programs.

<table>
<thead>
<tr>
<th>Author reference</th>
<th>Year</th>
<th>Topic</th>
<th>Trials patients</th>
<th>Conclusions (data are hazard, risk or odds ratios with 95% confidence intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inglis SC22,34</td>
<td>2011</td>
<td>Usual care compared with: <em>Structured telephone support (STS)</em> <em>Home telemonitoring (HTM)</em></td>
<td>30 trials 9805 patients</td>
<td>HTM reduced all-cause mortality [0.66; 0.54-0.81; ( P=0.0001 )]: STS showed a similar trend [0.88; 0.76-1.01; ( P=0.08 )]. Both HTM [0.79; 0.67-0.94; ( P=0.008 )], and STS [0.77; 0.68-0.87; ( P=0.0001 ]) reduced HF hospitalizations. Both interventions improved QoL, reduced costs, and were acceptable to patients. Improvements in prescribing, patient-knowledge and self-care, and functional class were observed</td>
</tr>
<tr>
<td>Savard LA35</td>
<td>2011</td>
<td>Meta-review of meta-analyses of disease management programs (DMP)</td>
<td>15 meta-analyses</td>
<td>Overall quality of existing reviews is mixed and fails to adequately acknowledge program diversity. It may not be possible to undertake rigorous meta-analyses of such diverse interventions</td>
</tr>
<tr>
<td>Shepperd S36</td>
<td>2010</td>
<td>The effectiveness of discharge planning (mostly for HF)</td>
<td>21 trials 7234 patients</td>
<td>LOS (-0.91; -1.55 to -0.27 days) and readmissions (0.85; 0.74 to 0.97) were reduced by discharge planning. For elderly patients with a medical condition (usually HF) there was insufficient evidence for a difference in mortality (1.04; 0.74 to 1.46). In 3 trials patients allocated to discharge planning reported in increased satisfaction. Little evidence on overall health care costs</td>
</tr>
<tr>
<td>Davies JE37</td>
<td>2010</td>
<td>Exercise rehabilitation for HF with left ventricular systolic dysfunction</td>
<td>19 trials 3647 patients</td>
<td>No impact on all-cause mortality or overall hospital admissions. HF-related hospitalizations were lower [0.72; 0.52-0.99] and HRQoL improved with exercise training</td>
</tr>
<tr>
<td>Taylor SJC38</td>
<td>2009</td>
<td>The effectiveness of different DMPs for patients with HF <em>Multidisciplinary teams (MDT)</em> <em>Case management (intense monitoring after discharge often by telephone and home visits)</em> <em>Specialist clinic interventions</em></td>
<td>16 trials 1627 patients</td>
<td>Case management tended to reduce all-cause mortality [0.86; 0.67 to 1.10, ( P=0.23 )] especially in better quality studies [0.68; 0.46 to 0.98, ( P=0.04 )]. There was weak evidence that case management may reduce admissions for HF. The effective components of the case management interventions are unclear. The single RCT of a multidisciplinary intervention showed reduced HF-related readmissions in the short term. There is little available evidence to support clinic-based interventions</td>
</tr>
<tr>
<td>Kozak AT39</td>
<td>2007</td>
<td>Effect of nonpharmacologic intervention and influence of face-to-face contact and duration of DMP on outcomes</td>
<td>26 trials ( \approx 4500 ) patients</td>
<td>Intervention was associated with reduction in HF hospitalizations [0.41; 0.30-0.5] and death 0.69; 0.56-0.86]. Face-to-face contact was associated with greater effect [0.42; 0.22-0.81; ( P&lt;0.05 ) and 0.63; 0.44-0.91; ( P&lt;0.05 )]. Longer treatment duration (≥12 months) was associated with a 65% reduction in HF hospitalizations and a 36% reduction in mortality</td>
</tr>
<tr>
<td>Jovicic A40</td>
<td>2006</td>
<td>Patient self-management (PSM)</td>
<td>6 trials 857 patients</td>
<td>PSM decreased all-cause readmissions [0.59; 0.44 to 0.80; ( P=0.001 )] and HF readmissions [0.44; 0.27 to 0.71; ( P=0.001 )], but not mortality [0.93; 0.57 to 1.51]. Adherence to prescribed medical advice improved, but there was no difference in functional capacity, symptoms, or QoL. The reported savings ranged from $1300 to $7515 per patient per year</td>
</tr>
<tr>
<td>Gohler A41</td>
<td>2006</td>
<td>DMP Explain heterogeneity in trial results</td>
<td>36 trials 8341 patients</td>
<td>Mortality reduced by DMP by 3% ( P=0.01 ) and rehospitalization by 8% ( P=0.0001 ). Factors explaining heterogeneity between studies included severity of disease, proportion of ( \beta )-blocker, country, duration of follow-up, and mode of contact</td>
</tr>
<tr>
<td>Yu DSF</td>
<td>2006</td>
<td>DMP</td>
<td>21 trials ≈4500 patients</td>
<td>Eleven of 21 trials of DMP were “positive.” Effective DMP was multifaceted and consists of an in-hospital phase, intensive patient education, self-care supportive strategy, optimization of medical regimen, and ongoing surveillance and management of clinical deterioration. Specialists should be involved and a flexible approach should be adopted</td>
</tr>
<tr>
<td>Roccaforte R</td>
<td>2005</td>
<td>DMP</td>
<td>33 trials 5308 patients</td>
<td>Mortality reduced by DMP [0.80; 0.69-0.93; P=0.003]. All-cause and HF-related hospitalization rates were also reduced [0.76; 0.69-0.94; P&lt;0.00001 and 0.58; 0.50-0.67; P&lt;0.00001], respectively. Different DMP approaches appeared to be similarly effective</td>
</tr>
<tr>
<td>Holland R</td>
<td>2005</td>
<td>The impact of multidisciplinary interventions on hospital admission and mortality</td>
<td>30 trials 7532 patients</td>
<td>Multidisciplinary interventions reduced all-cause admission [0.87; 0.79 to 0.95; P=0.002], mortality [0.79; 0.69 to 0.92; P=0.002], and HF admission [0.70; 0.61 to 0.81; P=0.001]</td>
</tr>
<tr>
<td>Phillips CO</td>
<td>2005</td>
<td>Whether a hierarchy of effectiveness exists with respect to complexity of published protocols of HF DMP specialist nurse-led HF clinics</td>
<td>6 trials 949 patients</td>
<td>DMP tended to reduce readmissions [0.91; 0.72, 1.16] and mortality 0.80 [0.57, 1.06], and the composite of death/hospitalization [0.88; 0.74, 1.04]. Better outcomes for DMP with discharge planning; readmission 0.30 [0.04, 2.60], mortality 0.96 [0.63, 1.47], composite 0.61 [0.18, 2.02], HF readmission 0.09 [0.10, 0.65] and hospital days/patient -0.26 [-0.49, -0.02] vs +0.09 [-1.17, +1.34]</td>
</tr>
<tr>
<td>Phillips CO</td>
<td>2004</td>
<td>Discharge planning plus postdischarge support</td>
<td>18 trials 3304 patients</td>
<td>Intervention reduced readmissions from 741 to 555 [0.75; 0.64-0.88]. Trend to lower mortality [0.87; 0.73-1.03], similar LOS [5.4 vs 8.5 days], greater improvement in QOL score [26%; 11-40% vs 14%; 5-20%; P=0.01], and similar or lower costs [-$359;-$763 to $45]</td>
</tr>
<tr>
<td>Gonseth J</td>
<td>2004</td>
<td>DMPs</td>
<td>27 trials ≈4500 patients</td>
<td>DMP reduced readmission for HF or cardiovascular disease [0.70; 0.62-0.79], all-cause readmission [0.88; 0.79-0.97] and the composite [0.82; 0.72-0.94]. The results displayed no substantial variation when only DMPs with home visits, outpatient visits to a clinic, or patient follow-up longer than 6 months were included</td>
</tr>
<tr>
<td>Gustafsson F</td>
<td>2004</td>
<td>HF Specialist Nurse Clinics</td>
<td>18 trials &lt;3000 patients</td>
<td>Reduction in hospital readmissions. Concluded that HF clinics using nurse intervention should be an integral part of the care of patients with HF</td>
</tr>
<tr>
<td>Gwadry-Sridhar FH</td>
<td>2004</td>
<td>Multidisciplinary heart failure management programs</td>
<td>8 trials 1300 patients</td>
<td>Readmissions reduced [0.79; 0.68-0.91; P&lt;0.001]. No effect on mortality [0.98; 0.72-1.34]. Data insufficient to investigate effects on QoL or compliance</td>
</tr>
<tr>
<td>McAlister FA</td>
<td>2004</td>
<td>Heart failure management strategies</td>
<td>29 trials 5039 patients</td>
<td>MDT reduced mortality [0.75; 0.59 to 0.96], HF hospitalizations [0.74; 0.63 to 0.87] and all-cause hospitalizations [0.81; 0.71 to 0.92]. PSM reduced HF hospitalizations [0.66; 0.52 to 0.83] and all-cause hospitalizations [0.73; 0.57 to 0.93], but had no effect on mortality [1.14; 0.67 to 1.94]. STS reduced HF hospitalizations [0.75; 0.57 to 0.99], but not mortality [0.91; 0.67 to 1.29] or all-cause hospitalizations [0.98; 0.80 to 1.20]. In 15 of 18 trials that evaluated cost, MDT strategies were cost-saving</td>
</tr>
</tbody>
</table>

DMP, disease management program; HF, heart failure; HRQoL, health-related quality of life; HTM, home telemonitoring; LOS, length of stay; MDT, multidisciplinary team; PSM, patient self-management; QoL, quality of life; RCT, randomized controlled trial; STS, structured telephone support.
Patients admitted to hospital with heart failure (about 800 patients per year) or prescribed a loop diuretic (about 2500 per year) for any reason other than renal failure have plasma concentrations of NT-proBNP checked. Most of these patients are managed on upwards of 40 different general medical or surgical wards, which renders coordinated care difficult. Those with elevated values are reviewed by one of a small team of heart failure specialist “discharge-liaison” nurses that ensure that appropriate investigations are done and that those with confirmed heart failure receive specialist input.

All patients with confirmed heart failure are considered for home telemonitoring, with priority given to those considered unstable and at high risk of hospitalization or death. A new generation of systems is being developed through the Heart-Cycle Program (FP7-216695; European Union 7th Framework Program). Home telemonitoring systems link the patient’s television with equipment to monitor weight, blood pressure, and heart rate and rhythm. Patients are asked to complete questions on their television screens about symptoms and get questions to check that they know how to contribute to their personal management. They are then advised which educational videos they should watch, but can select from a whole variety. The system paces the patient’s education, but patients can choose to go faster and can repeat educational sessions as often as they wish and with friends and relatives. Patients are encouraged to get into a regular 15-minute morning habit of telemonitoring activities. Patients are remarkably compliant and successful once they know what to do. The provision of feedback in terms of trend charts for weight and blood pressure gets patients much more engaged with their care. New motivational programs and sensors will make the technology more and more efficient and effective. The development of therapeutic algorithms allows patients to make many decisions about the need for repeat measurements of weight or blood pressure, changes in medication, and the timing of blood tests. The system and the patient can deal with up to 70% of the issues generated by conventional telemonitoring systems, relieving health professionals from a substantial workload, which greatly improves work efficiency and effectiveness.

A telemonitoring nurse, supported by the “discharge-liaison” nurses, provides daily support for up to 250 telemonitored patients. The system deals with about 70% of issues such as out-of-range measurements and need to adjust diuretic sodium, diuretic dosage, and titration of ACE inhibitors and β-blockers. It also provides advice and support to health professionals. The aim is to maintain the patient in an ideal symptomatic and hemodynamic range that, compared with a strategy of crisis detection and management, is much more likely to modify the natural history of disease favorably. The system also sifts the data received to identify patients that are running into trouble and that require intervention from a health professional. Stable patients may only require a health professional to review telemonitoring data once every 6 to 8 weeks.

A small team of heart failure specialist community nurses can be directed by the telemonitoring nurse to patients that are running into trouble and require additional support. Community volunteers provide an extra layer of support. Older patients sometimes require more coaching with the equipment and some even require help to make measurements. With a modest amount of training, the voluntary sector can assist some of the most frail and vulnerable patients benefit from telemonitoring.

Currently, patients are offered 4 months of telemonitoring. At that time they are reevaluated. Patients who are considered still unstable or at high risk of events are offered a further 4-month cycle. Patients who are stable are offered the choice of whether to continue or not. About 10% of patients have poor compliance with tests, and telemonitoring is usually withdrawn from these patients after discussion with a specialist nurse who has identified no obvious remediable action that could improve engagement.

In conclusion, patients themselves are a huge potential health care resource that has not been tapped into as yet. The future is home telemonitoring and electronic patient records for those who have chronic disease who wish to have the best chance of improving their quality and quantity of life. Clearly, some will disagree—mainly those who don’t have a severe chronic illness and perceive technology to be intrusive and impersonal. From patients with serious illnesses, who often feel lonely and frightened, the recurrent theme is that they feel like these technologies are their “guardian angel” and their “lifeline.” Rather than isolating patients, they draw them back into society. Patient education and support need to be maintained throughout the patient’s life as withdrawal of support appears associated with adverse outcomes.

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Keywords: heart failure; patient education; systematic review
L'éducation est une composante vitale du traitement pour améliorer l’état des patients atteints d’insuffisance cardio- 
dique. Ceux qui ne connaissent pas bien leur maladie et leur traitement sont sévèrement désavantagés, comme le 
montrent les taux plus élevés d’hospitalisation et de mortalité. Les patients devraient jouer un rôle actif dans la prise 
en charge de leur santé. L'éducation efficace des patients et des soignants nécessite une approche d’équipe pluri-
disciplinaire et doit insister sur l’adhésion au traitement, les recommandations concernant le style de vie et l’aide aux 
patients pour reconnaître les signes et symptômes traduisant la progression de la maladie. Cet article examine l’ap-
proche de l’éducation du patient, les obstacles possibles à son apprentissage et quelques stratégies pour l’aider à 
surmonter ces obstacles. Il est vraisemblable que les systèmes de télésurveillance domestique joueront un rôle vital 
dans la prise en charge de l’insuffisance cardiaque et dans la plupart des autres pathologies médicales de longue 
durée.
Can the target doses of medications such as those defined in morbidity-mortality trials in heart failure patients be realistically achieved in clinical routine?

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Numerous observational studies have demonstrated that "real life" heart failure (HF) patients receive lower medication doses than the targets recommended in guidelines. The problem is more widespread for β-blockers than for angiotensin-converting enzyme inhibitors because of their many contraindications and side effects. Even in outpatients treated by cardiologists, only 18% to 21% actually receive target doses of β-blockers.1

The low incidence of optimal uptitration is partly due to differences between patient populations in real life and randomized trials. Real-life patients are much older, with higher incidences of severe HF with low blood pressure and concomitant somatic diseases, general fragility, and psychiatric diseases/dementia. The main independent predictor of β-blocker undertitration is age.2 Observational studies report that low heart rate (HR) at rest is not a limiting factor in achieving target dose, however. Another reason for undertitration is overestimation of the risk of side effects. In a comparatively small (n=169) prospective randomized trial,3 the use of supervised nurse facilitators when initiating and titrating β-blockers resulted in 43% reaching target doses, compared with 10% in usual practice. Thus, achievement of guideline-recommended target doses in clinical practice, at least for β-blockers, appears unrealistic.

At least two questions arise: to what extent is the clinical effect of β-blockers dose dependent in HF? How sound is the use of empirically chosen target doses? There are few large, multicenter, prospective randomized dose-ranging β-blocker trials with clinical end points. In the small (n=345) randomized Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA), treatment with carvedilol was associated with a small dose-related improvement of ejection fraction and survival. Both parameters, however, were not prespecified end points. Importantly, HR reduction at all three doses was dose related, though minimally.

In a retrospective subgroup analysis in Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF), compared with placebo, relative reduction in mortality was the same in patients uptitrated to metoprolol ≤100 mg and >100 mg daily, and associated with identical on-treatment and basal HR.

Similar results were obtained in a retrospective subgroup analysis of patients enrolled in Cardiac Insufficiency Bisoprolol Study II (CIBIS II). No significant differences were found in baseline, final, and absolute HR reduction with three doses of bisoprolol.4

A meta-analysis demonstrated that the survival benefit of β-blockers in HF patients is associated with magnitude of HR reduction but not drug dose.5 For every 5 beats per minute (bpm) HR reduction, there was an 18% reduction in risk of death.

The notion of HR as a risk factor and intervention target in HF was confirmed in Systolic Heart Failure treatment with the ß-blocker ivabradine Trial (SHIFT).6 HR reduction with the selective ß1 channel blocker ivabradine in patients with sinus rhythm >70 bpm was associated with an 18% reduction in cardiovascular death and hospitalization for HF (primary end point), although without influencing cardiovascular and all-cause mortality. All patients received optimal treatment, including maximal tolerated β-blocker doses. The comparative clinical effect of pure HR reduction versus inhibition of all sympathetic stimulation by β-blockade in HF patients can only be obtained through specially planned prospective randomized trials directly comparing the two strategies.

In the meantime, it seems reasonable to consider that the target dose of β-blocker in HF is not a fixed dose, but the maximal tolerated dose or dose needed to lower sinus rhythm to 60-70 bpm at rest. The latter is probably a pathophysiologically sound target. If this target isn’t reached at the maximal tolerated β-blocker dose, which is what happens in the majority of real life patients, the evidence-based treatment strategy should be the addition of ivabradine.

References
Among the obstacles to guideline implementation are the general resistance to changing patterns of practice, loss of professional autonomy, concern about litigation, potential economic disincentives, inadequate skill sets, lack of technological support, the “does not apply to my patient” mindset, and an out of date/moving target. Another limiting factor is patient preference in treatment decisions, which is a challenge for doctors.

With regard to HF, although physicians are increasingly encouraged to apply guidelines in their practice, it has repeatedly been observed that a considerable proportion of patients do not receive evidence-based treatment. Additional factors to explain this could be lack of knowledge, expertise, and time, and the concept that trials enroll highly selected patients.

One additional challenge in the implementation of guidelines in clinical practice is use of the recommended dose, or the doses that showed benefit in trial patients. One study found that patients who would be eligible for trials were being treated with at least half the target dose, and 40%-50% were receiving the minimum dose recommended by regulatory authorities. With regard to beta-blockers, 54% of patients eligible for Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF) received a beta-blocker, of whom 20% received at least half the target dose, and only 6% received the full target dose. In a subgroup of the aforementioned trial-eligible patients, barely half were prescribed a beta-blocker, with doses lower than those proven to be effective in large controlled trials. Lack of similarity between HF patients in clinical practice and clinical trials thus does not adequately explain undertreatment of therapy.

Obstacles to use of target doses of beta-blockers include the need for close care, progressive up titration in treatment of HF, repeated assessments to monitor individual responses, and an effective HF follow-up program. Symptoms of HF such as hypotension, dyspnea, and weakness during exercise can be confused with side effects of beta-blockers. Treatment with beta-blockers can provoke an initial worsening of symptoms. Doctors may consider introduction or up titration of beta-blockers to be a cause of decompensated HF during hospitalization. Doctors may already be satisfied with the symptomatic improvement with smaller doses of drugs, and therefore not push for the higher targets in order to avoid adverse events. The result is that doctors in clinical practice do not prescribe or patients are not using—optimal doses of beta-blockers.

The question is whether to persist only in the implementation of guideline-recommended doses, or to accept the real world and look for additional therapies.

Logically, the initial impetus is only to develop strategies to improve adherence to guideline-recommended doses. Many publications have shown the limitations of this strategy, however, although this initiative should never be abandoned. In real life, nevertheless, alternative and additional treatments should be investigated to resolve this difficult issue. The recent publication concerning the effects of ivabradine on HF, which showed a reduction in hospital admissions for worsening HF and deaths due to HF, is a positive and important example.

In summary, the prescription of target doses is very important in the treatment of HF. However, in the real world, the association of new effective drugs and treatment strategies should form an additional therapeutic approach. ■

References
Chronic heart failure (CHF) is a condition characterized by unpleasant symptoms, high mortality, and recurrent and lengthy hospitalizations. It is a major public health concern of growing prevalence. The short-term goals of CHF management are directed toward relieving symptoms and improving functional capacity and quality of life. Long-term goals include reducing mortality and slowing or reversing the underlying cardiac structural abnormalities associated with CHF. Two decades of controlled clinical trials have led to significant developments in the treatment of heart failure. The results of these large placebo-controlled randomized trials have been integrated into European and US treatment guidelines. These guidelines emphasize in particular the beneficial effects on mortality and morbidity of angiotensin-converting enzyme (ACE) inhibitors, β-blockers, angiotensin II receptor blockers (ARBs), and aldosterone antagonists. However, several national and international surveys consistently suggest there is suboptimal utilization of recommended medications in outpatients, as well as in hospital situations. One reason for this could be that CHF remains underdiagnosed and undertreated. Undertreatment may mean either underuse of modern recommended treatments, or prescription of low doses of these drugs.

A survey performed to assess awareness of CHF management recommendations in Europe among cardiologists, internists, geriatricians, and primary care physicians showed that although each physician group lacked complete adherence to guideline-recommended management strategies, they were used significantly less well by internists, geriatricians, and primary care physicians, indicating the need for education of these essential health care providers. The EuroHeart Failure Survey, performed in 116 hospitals across 24 European Society of Cardiology countries, showed suboptimal utilization of ACE inhibitors and β-blockers—particularly the latter. The Impact-Reco study, which compared heart failure management strategies before and after publication of updated heart failure guidelines by the European Society of Cardiology, found a significant improvement post publication. Analysis of the reasons for nonprescription or for not reaching target doses suggested that advanced age (>75 years), contraindications, comorbidities such as renal failure, and side effects all played major roles.

Interestingly, use and dosage of evidenced-based drugs in the treatment of CHF is influenced by patient, but also physician, gender. The gap between guideline recommendations and clinical routine is an important issue; suboptimal treatment should be avoided by all physicians involved in the care of CHF patients. However, when considering whether everyday practice is suboptimal, an important question arises: is more always better, and should dosage recommendations be followed in all patients? Although it is recommended that doses be uptitrated to high target levels as defined in the original trial protocols, the superiority of high versus low-to-moderate doses of these drugs in reducing CHF mortality has not been documented convincingly. The reduction in total mortality, sudden death, and death from worsening heart failure was in the same range in two major β-blocker trials Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF) and Cardiac Insufficiency Bisoprolol Study II (CIBIS II).

Furthermore, the combination of ACE inhibitors and ARBs showed no clear clinical advantage, but increased the risk of adverse effects such as symptomatic hypotension, worsening renal function, and hyperkalemia. There are also well-known data documenting increased risks with higher doses of digoxin, diuretics, and spironolactone.

In conclusion, guideline-recommended doses of drugs remain the scientifically validated basis for treatment in all patients with CHF. The additive therapeutic effects of β-blockers and ACE inhibitors can improve prognosis regardless of age and comorbid conditions. However, instead of dogmatic enforcement of high target doses, the dose should be adapted individually, taking into consideration particular characteristics of certain patient subpopulations. Low initial doses and slower uptitration will improve the acceptance of heart failure drugs, thus enabling a more accurate application of the guidelines.

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**Beta-blockers form an essential part of the standard care of patients with systolic chronic heart failure, and current guidelines recommend up titration to the target dose in order to maximize therapeutic benefit.**¹ This recommendation is based on high-quality clinical data supporting a dose-dependent beneficial effect of these agents on patient prognosis.²⁻⁶ However, beta-blocker target doses are often difficult to achieve in clinical routine; in fact, they have even proven difficult to achieve in the clinical trial setting. In the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), the mean daily dose of study drug in the metoprolol group was 159 mg once daily, with (only) 64% of patients receiving the target dose of 200 mg once daily. Similar or lower target-dose rates were achieved in further landmark trials such as Effect of Carvedilol on Survival in Severe Chronic Heart Failure (COPERNICUS), Cardiac Insufficiency Bisoprolol Study II (CIBIS II), and Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS).²⁻⁶ Of note, reasons for not reaching target doses, or even discontinuing beta-blockers in heart failure patients, often remained obscure. For example, in SENIORS, the main reason for discontinuation of nebivolol was reportedly “patient’s decision” (10% patients).⁵ As expected, beta-blocker target-dose rates are even lower in the “real world.” A national cohort study in the UK revealed that less than 40% of heart failure patients were treated with a beta-blocker, and less than 20% treated with a guideline-recommended agent achieved target dose. As in clinical trials, the reasons for not being treated with a beta-blocker or achieving target dose remained obscure for a large proportion (>50%) of patients.⁵

There are several possible reasons for beta-blocker undertreatment, poor tolerance being most commonly reported. Besides bradycardia and hypotension, beta-blockers may cause fatigue, depression, and erectile dysfunction. Patients experiencing beta-blocker-related undesirable effects at the initiating dosage are very likely not to tolerate target doses. Persistence in the prescription of higher doses in such cases will result in discontinuation or poor adherence. Thus, what represents the optimally efficacious and safe beta-blocker dose for an individual patient with heart failure may not necessarily be the dose dogmatically extrapolated from clinical trials.

An important part of the beneficial effect of beta-blockade in heart failure is attributed to heart rate reduction. A clear relationship between change in heart rate with beta-blockers and all-cause mortality has been demonstrated in heart failure patients. This concept is supported by the recently published Systolic Heart failure treatment with the I, inhibitor ivabradine Trial (SHIFT), assessing the effect on heart failure outcomes of heart rate reduction by the selective sinus-node inhibitor ivabradine.⁶ In SHIFT, 90% of study participants were treated with a beta-blocker, but only 23% reached the target dose. This target dose percentage is clearly far from optimal, but it does reflect “real world” management of heart failure. Ivabradine administration on top of beta-blocker resulted in (further) heart rate reduction, and apparently in a significant reduction in the primary end point of cardiovascular death or hospital admission. SHIFT thus supports the use of ivabradine to reduce major risks associated with heart failure in patients receiving guidelines-based treatment.

In conclusion, registries, national surveys, and even randomized controlled clinical trials suggest that achieving what has been defined as beta-blocker target doses is a utopia in the clinical practice of heart failure management. Targeting heart rate reduction by a dual-drug regimen that respects the patient’s tolerance and (perceived) well-beings appears, based on the results of SHIFT, to be the best strategy to achieve better compliance and outcome in terms of mortality and morbidity.

**References**

Guideline authorities mandate lifesaving drugs for the treatment of heart failure (HF), to be given at target doses used in definitive outcome trials establishing their benefit.1,2 However, it is clear that in everyday clinical practice, physicians and patients are unwilling or unable to achieve target doses. This has been well established from epidemiological datasets, and also evaluation of background therapy in randomized clinical trials of new therapies.3,4 These observations raise two key questions: (i) can optimal dosing actually be achieved in routine clinical practice?; and (ii) does it really matter whether it can be achieved?

Concerning the first question, in the recent Systolic Heart failure treatment with the I receptor blocker ivabradine Trial (SHIFT),4 where dose of background β-blocker was critical to interpretation of the results and optimal use strongly encouraged, only 26% of patients were able to reach target dose of β-blocker. Reasons given for not being able to reach target dose reflected the real world, with hypotension and fatigue the predominant explanations. Additionally, 11% of participants did not receive a β-blocker because of chronic obstructive pulmonary disease/asthma, hypotension, or other factors. Nevertheless, 56% of patients reached at least 50% of target dose. This leads to the second question of whether it actually matters. It seems the answer depends on the drug class. For β-blockers, there is only limited evidence from dose-ranging studies focused on surrogate end points like ventricular function. Nevertheless, in Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA), higher doses were more effective on ventricular remodeling, and major events were lower at higher doses (although there were more withdrawals for adverse events). Studies of angiotensin-converting enzyme inhibitors have largely failed to show a true dose response for major cardiovascular outcomes. In Assessment of Treatment with Lisinopril and Survival (ATLAS), despite a large dosing differential between low and high doses of lisinopril, there was only a very small, borderline significant, effect on the combined death and HF hospitalization end point and no significant impact on all-cause mortality. The recent Heart Failure End Point Evaluation of Angiotensin II Antagonist Losartan (HEAAL) study of high- versus low-dose losartan suggested that higher doses may have greater benefit, at least on the primary combined morbidity/mortality end point, if not death alone, but with more adverse events. On this basis, guideline recommendations remain that patients and physicians aim to reach target dose. However, with increasing personalization of therapy, the issue arises as to whether there are better approaches to maximizing drug efficacy than target dose alone. Heart rate (HR) is thought to be an important component of the therapeutic benefit of β-blockers5 (reinforced by the recent SHIFT HR analysis).6 If so, perhaps titration of dosage according to change in HR (or achieved HR) may be a more logical approach to their administration. Similarly, for drugs that manipulate neurohormonal systems, titrating to a target specific to the system manipulated (or a general target like plasma brain natriuretic peptide [BNP]) may be more logical than following generic dosing recommendations. A further consideration is the “cost” of higher doses in terms of increased drug-related adverse events. Finally, the emerging ability to rapidly delineate the individual genomics and proteomics of the patient may assist with greater individualization of drug choice and dosage.

All of that is for the future. For the present, we are left with a situation in which patients cannot reach target doses despite strong guideline recommendations. Clearly education is still required among prescribers to optimize achievable doses of HF drugs. Nevertheless, there would still be a significant percentage of patients who cannot reach target dose. This matters at the population level, but does it matter for the individual? We are at present unfortunately unable to definitively answer that question.

References
Chronic heart failure is a major public health problem, and is associated with high morbidity and mortality. A number of large double-blind controlled trials in the last three decades have provided evidence for the efficacy and safety of a number of pharmacological treatments for heart failure. The cornerstone of pharmacological treatment is the use of β-blockers and angiotensin-converting enzyme inhibitors. Based on the drug dosages used in the aforementioned large trials, major guidelines on heart failure—including the updated guidelines from the European Society of Cardiology and the American College of Cardiology/American Heart Association—recommend titration of the doses of these agents to the target dose used in the clinical trials. A number of studies have revealed, however, that a significant number of patients receive doses of these medications that are lower than the target doses. The EuroHeart Failure Survey reported that on average, the daily dosage of β-blocker was far below target doses. In the Impact-Reco II Program, 23% of patients received the target dose, and 54% received 50% or more of the target dose. In the Systolic Heart failure treatment with the If inhibitor ivabradine Trial (SHIFT), 56% of patients on β-blockers were treated with at least 50% of the target dose, and 26% reached the target dose.

Common reasons given by physicians for patients not receiving target doses are hypotension, fatigue, and in the case of β-blockers, bronchospasm (especially in smokers).

The target doses of medications, particularly β-blockers, defined in morbidity-mortality trials in heart failure patients, may therefore be difficult to achieve in a significant proportion of patients in clinical routine. Moreover in a meta-analysis of β-blocker trials in heart failure, no significant relationship between all-cause mortality and β-blocker dosing was observed, and the benefit on mortality was related to the heart rate reduction achieved in each individual trial.

The recent SHIFT, which showed that heart rate reduction with ivabradine reduced clinical events in heart failure in relation to the heart rate achieved, confirms that heart rate is a risk factor in heart failure, and suggests that guidelines on heart failure may now need to consider heart rate reduction as a target for treatment.

**Further reading**

This is not only a medical question, but a philosophical one. What does “target dose” mean for clinical practitioners? Taking into account the magnitude of the problem and the space for discussion, I will discuss this using the example of β-blocker dosing in chronic heart failure (CHF) patients. Recommendations for optimal doses usually come from randomized clinical trials. But optimal doses often differ in clinical trials, so it is not easy to interpret data.

Officially, target doses of bisoprolol 10 mg/day, metoprolol 200 mg/day, and carvedilol 25 mg twice daily are recommended for CHF patients. These are based on results from Cardiac Insufficiency Bisoprolol Study II (CIBIS II), Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF), and Effect of Carvedilol on Survival in Severe Chronic Heart Failure (COHERINicus). However, practitioners are often afraid of β-blocker side effects and use substantially lower doses due to concerns for patient safety. Race, sex, age, body weight, liver and renal function, disease severity, and metabolism are all important when considering the abstract “target dose.”

Post hoc analysis of MERIT-HF revealed that patients tolerating >100 mg daily or <100 mg daily of metoprolol had the same heart rate (HR) decline and similar improvement in mortality and hospitalization. In CIBIS II, only 42% reached 10 mg bisoprolol, while 33% stayed on doses of 1.25-3.75 mg. As in MERIT-HF, patients on the lowest doses were older with more severe CHF, lower blood pressure, and concomitant complications. Doctors were simply afraid to uptitrate the β-blockers in these patients! Again, significant morbidity and mortality reduction was reached with all doses.

In a recent meta-analysis, it was clear that HR decline during treatment should be taken into account for optimal CHF treatment. Of course, modern recommendations are that doctors should uptitrate β-blockers, balancing the usefulness against possible harm. Systolic Heart failure treatment with the I1 inhibitor ivabradine Trial (SHIFT) showed that HR reduction with ivabradine, which decreases HR without affecting blood pressure and conduction, plus β-blockers, resulted in morbidity and mortality improvement in CHF patients. Is this a result of ivabradine itself, or just HR decrease? If the latter, is it possible to gain the same result just by uptitrating β-blockers? In terms of evidence-based medicine, this question will be unanswered until a trial compares uptitration of β-blockers with combination of β-blockers and ivabradine.

It is important to understand whether CHF patients receiving ivabradine were already on an optimal dose of β-blocker where they failed to reach an optimal HR of below 70 beats per minute. In Morbidity-mortality Evaluation of the I1 Inhibitor Ivabradine in Patients With Coronary Artery Disease and Left Ventricular Dysfunction (BEAUTIFUL), nearly 90% of patients with coronary artery disease and left ventricular dysfunction received mean β-blocker doses <50% of the recommended dose. In EuroHeart Failure Survey, we see practically the same mean β-blocker doses in clinical routine in 13 European countries. In SHIFT, 56% of patients received >50% of the maximal dose, and 26% reached the optimal β-blocker dose. This is still well above clinical practice. In a recent Swedish registry, for example, only 10.8% of patients received target doses of β-blockers, and only 20.6% received >50% of the maximal dose.

So we can conclude that normally practiing doctors use about half the target dose of β-blocker in CHF treatment, and administration of ivabradine doesn’t change this practice. Although we must try to uptitrate, there is no real possibility of reaching recommended target β-blocker doses in the near future in clinical routine. In a Russian registry, 46% of patients receiving β-blockers didn’t reach the recommended HR of <80 beats per minute. Thus, administration of medications that reduce HR and are not contraindicated with β-blockers could be useful for the successful treatment of CHF.

Further reading
Over the last two decades, there have been significant advances in the pharmacological management of heart failure. Large international clinical trials have demonstrated the impressive impact of β-blockade and therapies modulating the renin-angiotensin-aldosterone system in improving the outlook for patients with reduced ejection fraction heart failure. Beyond clinical trials, the remaining challenge is to apply these advances in the most effective manner to the general heart failure population. This critical last step in the process poses some questions and challenges.

As a result of the large body of evidence from clinical trials, guidelines have been developed that outline a best-practice approach to the pharmacotherapy of heart failure. The purpose of these guidelines is to improve the overall adherence to what is felt to be “best practice.” They recommend stepwise incremental dose increases of these proven agents, with the aim of achieving clinical trial doses. However, several surveys have demonstrated disappointing application of this guideline approach in clinical practice.

There are two major reasons for the less than impressive uptake of the guideline approach. The differences between clinical trial populations and the community heart failure patients have been well described. The latter tend to be on average a decade older, are more likely to be female, and have a greater number of comorbidities, especially those that may alter drug metabolism. As a result, many experienced practitioners, while accepting the evidence base of guidelines, are of the opinion that they need to be applied cautiously in the community population, and that single-mindedly striving for clinical trial doses may not have the same benefit as observed in trials. Indeed, some feel that dogmatic adherence may in some cases exchange the symptoms of heart failure for those related to the treatment of the condition.

What is missing in present-day pharmacological management of heart failure to help guide how much therapy to apply is an objective indicator of when enough therapy has been applied. Natriuretic peptide is being increasingly used to titrate therapy to more effective levels, and may in the future be used on its own or in combination with other markers to show when sufficient therapy has been applied. Such attempts at individualization of therapy will be important in our efforts to improve application of therapy in an effective manner.

While this may explain some of the failure to apply guidelines, a more fundamental problem is the lack of a formal structure of care for patients with heart failure. It has been well demonstrated that physicians experienced in heart failure management apply proven therapies in a more effective manner. Furthermore, disease management programs led by specialist physicians have applied the necessary structure to encourage effective use of heart failure therapies. However, the majority of patients with heart failure do not receive this structure of care, reducing their likelihood of receiving best-possible pharmacotherapy.

Therefore, to encourage optimal application of guidelines to the community population, we need to encourage widespread use of disease management programs, and within this structure, assess the relative merit of proven therapies in each individual case. In doing so, it may emerge that in certain situations, striving for clinical trial dosing may be inappropriate, but at least this will be decided within a structure of care that attempts to bring best-possible therapy to the wider heart failure population.

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Globally, the prevalence of heart failure is increasing with aging of the population. Heart failure due to depressed systolic function is an important cause of morbidity and mortality. For many years, treatment consisted only of medications such as digitalis and diuretics. Since the late 1980s however, several landmark clinical trials have revolutionized the management of systolic heart failure with the introduction of neurohormonal blockade, and have clearly established the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-blockers, and aldosterone antagonists as standards of care. These agents have been shown to significantly reduce all-cause mortality, reduce hospitalizations, and improve quality of life.

All clinical guidelines recommend that patients with systolic heart failure be commenced on these classes of drugs, using the same agents that were tested in the randomized trials, in a similar manner, and at the same doses used. However, in real life, although these medications are initiated in the majority of patients with systolic heart failure, the doses used are often suboptimal and there is a reluctance to up titrate to target dose.\(^1,2\)

The reasons for this are multifactorial and are both patient related and doctor related. They include side effects such as symptomatic hypotension, bradycardia, worsening renal function, and hyperkalemia. Individuals — especially the elderly — get confused with the frequently changing dose schedule (from daily to twice daily, and from half a tablet to 1 tablet) and are thus unhappy to have their dose up titrated. Individuals whose doses are suboptimal (<50% of the target dose) have almost double the mortality of those who take ≥50% of the recommended dose.\(^1\) In fact, the highest-risk patients were found to have the lowest prescription rates for ACE inhibitors, ARBs, and β-blockers.\(^3\)

The majority of individuals in the community with systolic heart failure do not fulfill the entry criteria for enrollment into the randomized controlled trials. These include the elderly (over the age of 80 years), those with serum creatinine of more than 300 µmol/L, asthmatics, those with chronic obstructive airway disease, those with a history of sustained arrhythmias, those on antiarrhythmic drug therapy, and those having automatic implantable cardioverter defibrillators. Thus there is a lack of evidence-based knowledge on how best to treat these patients, the majority of whom can only tolerate suboptimal doses of ACE inhibitors (or ARBs), β-blockers, and aldosterone antagonists.

The recently published Systolic Heart failure treatment with the \(L\), inhibitor ivabradine Trial (SHIFT) provides some answers. When added on to standard heart failure medications at the doses that reflect practices in real life, ivabradine produced a statistically significant reduction in major cardiovascular events. Ivabradine produced a reduction in heart rate in patients who were unable to tolerate higher doses of β-blockers. It was well tolerated and there was only a single up titration—from 5 mg twice daily to 7.5 mg twice daily.\(^4\)

The challenge of the future is to find ways to address the “treatment gap” that exists in a majority of our patients.

References
Can target doses of medications be realistically achieved in clinical practice?

Current guidelines for the management of heart failure recommend uptitrating the doses of drugs to target doses defined in a number of morbidity and mortality trials. Long-term adherence to the recommendations in “real life” is disappointing, and the average dose of the majority of pharmacological treatments remains below the recommended dose. There are a number of factors responsible for this; ie, health systems, patients, physicians, and treatment factors (Table), with different levels of significance in certain patient subpopulations.

One of the most important issues in clinical practice is the lack of communication between physician and patient. Health systems worldwide are under increasing pressure to be time efficient and cost effective, resulting in patients not being allowed to admit that they cannot tolerate their medication and that they are simply not taking it. This denies the patient the opportunity to explore other better-tolerated treatment avenues with their physician. Treating the hypotensive stable patient with poor left ventricular contractility, but tachycardia remains a challenge. We are still miles away from patient-tailored therapy based on genetic profiling, and therefore dogmatic enforcement of guideline-based recommendations is controversial. Apart from mortality, even the end points for successful short-term and long-term outcomes are under debate. Heart rate is one of the most informative and simple parameters that can be measured in cardiovascular disease. However, it is often not taken in a standardized fashion; ie, body posture, duration of measurements, and environmental temperature are not taken into account.

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BARRIERS TO ACHIEVING MEDICATION TARGET DOSE IN HEART FAILURE PATIENTS AROUND THE WORLD

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11. B. D. Westenbrink, W. H. van Gilst, The Netherlands

Pharmacological therapy has dramatically improved heart failure (HF) morbidity and mortality, and remains the cornerstone in disease management. The efficacy of the expanding list of HF drugs has been established in meticulously controlled trials employing careful drug titration protocols aiming for the same target dose in all patients. Clinical practice guidelines therefore recommend titrating all HF patients to the target doses that were used in the original trial protocols. A recent European survey showed that most HF patients received appropriate drugs, yet only 25% were prescribed the recommended target dose. This prompts the question of whether 75% of HF patients are undertreated, or whether the target doses are unrealistic.

Aiming for a high target dose with an established safety profile and clear survival benefits appears both sensible and feasible. The superiority of higher over lower doses of several HF drugs has been established in direct comparisons and meta-analyses. In Assessment of Treatment with Lisinopril And Survival (ATLAS), a high lisinopril dose significantly improved analyses. In Assessment of Treatment with Lisinopril And Survival (ATLAS), a high lisinopril dose significantly improved outcome compared with a tenfold lower dose. Heart Failure End Point Evaluation of Angiotensin II Antagonist Losartan (HEAAL) reported similar findings with losartan in patients receiving contemporary background medications. Patients in the high-dose group experienced more side effects (mild), but discontinuation of the study medication was sparse and comparable between groups. Furthermore, with intense counseling and careful titration protocols, multidisciplinary HF clinics often manage to increase drug dosage. Bridging the gap between guidelines and clinical practice thus appears feasible, suggesting that guideline compliance can be improved.

There are, however, important differences between the general population and trial populations. A mere 13% of European HF patients would have met the inclusion criteria of several landmark trials. Patients with preserved ejection fraction, advanced age, significant comorbidities, and women were often excluded. While the efficacy of these drugs in the excluded population is not disputed, they do exhibit different pharmacokinetic and pharmacodynamic properties that limit extrapolation of dose recommendations. In Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS), which specifically included elderly patients, the target dose of nebivolol was tolerated in only 68%. A closer look at other landmark trials also reveals target doses often not tolerated. In Studies of Left Ventricular Dysfunction (SOLVD) and Effect of Carvedilol on Survival in Severe Chronic Heart Failure (COPERNICUS), for instance, the mean dose of the investigational drug was 56% and 74% of the target dose, respectively. Furthermore, in many trials, there were no restrictions on the dosage of background medications, suggesting that targets might have been met at the expense of lower doses of other drugs. If the target doses cannot be reached in trial participants, why should it be different in real life? Indeed, multidisciplinary HF programs may be successful in increasing dosages, but the actual target dose is seldom reached.

Dose titration is an essential component of effective pharmacotherapy, allowing us to establish the optimal dose for an individual patient. The large interindividual variations in dose response and toxicity necessitate a tedious titration process that requires commitment from patients and caregivers alike. The relatively low dosing of HF drugs in clinical practice suggests suboptimal dose titration that should be improved. Failure to achieve target doses does not necessarily result from negligence, since the target doses are often not tolerated even in the most controlled settings.

Thus, instead of dogmatically enforcing unrealistic targets and chastising physicians who fail to reach these goals, we should encourage titration of medication to the maximal tolerated dose in all HF patients. More may be better, but a little is better than too much.

References
Clinical advantages of Procoralan in cardiovascular prevention

by I. Elyubaeva, France

Cardiovascular death is the major cause of premature death in most countries. Further to the well-established importance of conventional risk factors, the role of heart rate (HR) is now better understood as a main determinant of myocardial ischemia and cardiac work, and as an important therapeutic opportunity, since it can be easily modified in clinical practice. Recent large randomized clinical studies have confirmed earlier epidemiological and clinical data in showing that resting HR is an independent cardiovascular risk factor in patients with coronary artery disease or heart failure. HR reduction is being increasingly recognized today as a valuable therapeutic approach in patients with acute or chronic coronary disease or with congestive heart failure. Procoralan is a selective HR-lowering agent, and the first agent of this type to be approved for therapeutic use. As opposed to other HR-lowering agents, Procoralan has a unique action on pacemaker activity in the sinoatrial node. Procoralan reduces HR through its selective and specific inhibition of the pacemaker I_{f} current, while avoiding any deleterious cardiovascular effects. Randomized clinical trials have established the clinical benefits of Procoralan in preventing angina and minimizing underlying ischemia both in monotherapy and in combination with other treatments, including β-blockers. The BEAUTIFUL trial (morBidity-mortality EvAlUaTion of the I_{f} inhibito ivabradine in patients with coronary disease and left ventricULar dysfunction) showed that, in addition to symptomatic improvement, Procoralan also improves clinical outcomes in symptomatic coronary patients or in those with a baseline heart rate ≥70 bpm. The recent results from SHIFT (Systolic Heart Failure Treatment with the I_{f} Inhibitor Ivabradine Trial) have significantly extended the range of clinical benefits of Procoralan by showing substantial reductions in main heart failure outcomes in patients with chronic heart failure. This evidence confirms Procoralan as having as an essential therapeutic role in improving the management of patients with coronary artery disease or heart failure.

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from epidemiological surveys or clinical registries have revealed that the majority of patients continue to have elevated HR in clinical practice. Insufficient attention is being given to HR control in routine practice, and β-blocker dosage is often suboptimal and seldom readjusted during long-term therapy. Very often the target dose of β-blocker is not reached because of intolerance or side effects such as fatigue, depression, bronchospasm, or erectile dysfunction. The inadequate control of HR in clinical practice means there is an important need for novel therapeutic modalities to remedy this missed opportunity and improve the management of patients with cardiovascular disease.

Procoralan is a selective HR-lowering agent, the first agent of this type to be approved for therapeutic use and the first of an entirely new therapeutic class. Its concept is based on the elucidation of the key role of the If current as the basic mechanism underlying the generation of spontaneous pacemaker activity. The If current, which is a mixed Na+-K+ current, determines HR by modifying the diastolic depolarization slope. It is also involved in the control of the spontaneous frequency of pacemaker cells, and thus HR, through the action of the sympathetic (accelerating) and vagal (slowing) systems. This makes the If current a natural target for pharmacological intervention aimed at HR control. As opposed to other HR-lowering agents, Procoralan has a unique action on pacemaker activity in the sinoatrial node of the heart. Through its selective and specific inhibition of the If pacemaker current, Procoralan reduces HR, providing all the benefits of HR reduction without any of the deleterious cardiovascular effects observed with other treatments.

Clinical benefits of Procoralan in the management of stable CAD

The optimal management of coronary artery disease (CAD) is based on achieving a dual goal: reducing myocardial ischemia and preventing cardiovascular events. HR plays an important role in the pathophysiology of CAD as a well-established determinant of ischemia. Elevated HR is now increasingly acknowledged as a prognostic factor. Thus, HR reduction has a clear role as a key therapeutic goal in patients with CAD, leading to better prevention of ischemia in the short-term and better prevention of cardiovascular events in the long-term.

Experimental data clearly support the anti-ischemic effects of Procoralan, which result from its action on both determinants of the oxygen balance: Procoralan reduces myocardial oxygen demand and improves myocardial oxygen supply by increasing diastolic perfusion time. The specific nature of HR-lowering with Procoralan fully distinguishes it from other HR-reducing therapies and explains its unique beneficial properties. In contrast to β-blockers, Procoralan does not alter left ventricular (LV) function and preserves isovolumic LV relaxation, thereby achieving the benefits of prolonged diastolic time while preserving the physiological mechanisms allowing adaptation to the exercise to take place.

The effect of Procoralan on coronary flow velocity reserve (CFR) in Skalidis et al study. Box-plots of coronary CFR at baseline (Baseline) and after 1 week’s Procoralan treatment, both at the intrinsic heart rate (Procoralan, [ivabradine]) and at a paced rate identical to that at baseline (ivabradine-pace). The effect of Procoralan on coronary flow velocity and coronary flow reserve was evaluated in a recent study in 21 patients with stable CAD who underwent coronary flow velocity measurements in a nonculprit vessel, using a Doppler guidewire, at rest and after adenosine administration to achieve maximal hyperemia. A significant increase in coronary flow reserve after short-term treatment with Procoralan (1 week) was reported.

Although resting coronary blood flow velocity returned to pretreatment values after HR correction, the enhancement of hyperemic coronary blood flow velocity reserve persisted. This means that the improvement in hyperemic coronary blood flow is not totally HR-dependent, and that it depends on the integrity (functional or structural) of the microcirculation. This study confirmed previous experimental data on the improvement in coronary hemodynamics with Procoralan. Improvement in coronary flow reserve has profound clinical implications since it predicts long-term cardiovascular outcomes.

The results of clinical trials are consistent with the role of HR in determining the frequency of angina and the severity of underlying ischemia as well as long-term ischemic outcomes. By reducing HR during exercise, Procoralan provides relief from symptoms of chronic stable angina. Benefits also accrue from the decrease in resting heart rate, which has been shown to reduce the risk of long-term cardiovascular events.
Data from randomized clinical trials and experience from daily practice provide strong proof of the clinical benefits of Procoralan and support its value in the management of patients with CAD.

**Antianginal and anti-ischemic efficacy of Procoralan**

Improvement in angina symptoms results in a significant improvement in quality of life, which is one of the essential goals of medical treatment. The substantial reduction in HR with Procoralan translates into antianginal and anti-ischemic benefits confirmed by the significant decrease in angina symptoms and short-acting nitrate consumption and improvement in exercise capacity observed both in monotherapy and in combination with other antianginal therapies such as the β-blockers.

**Reduction in angina attacks**

Procoralan substantially reduces the frequency of angina attacks and the consumption of short-acting nitrates compared with placebo: at the end of a 2- or 3-month open-label extension study, angina attacks decreased from 4.14±5.59 per week to 0.95±2.24 per week (P<0.001), while consumption of short-acting nitrates decreased from 2.28±3.74 units per week to 0.50±1.14 units per week (P<0.001).

At the end of the open-label treatment phase, patients underwent double-blind random assignment to continue on ivabradine or withdraw to placebo for 1 week. Frequency of angina attacks and short-acting nitrate consumption were unchanged among those patients who continued treatment with Procoralan, but increased in patients withdrawn to placebo.

The antianginal efficacy of Procoralan was confirmed in routine day-to-day practice in the large open-label, multicenter REDUCTION trial (not an acronym) conducted in a broad range of patients with stable angina. In this multicenter study, 4954 patients with stable angina pectoris received Procoralan for 4 months. Procoralan angina pectoris attacks decreased from 2.4±3.1 to 0.4±1.3 per week (P<0.0001). Consumption of short-acting nitrates decreased from 3.3±4.4 to 0.6±1.6 units per week (P<0.0001).

In the 344 patients treated concomitantly with β-blockers, angina pectoris episodes decreased from 2.8±3.3 to 0.5±1.3 per week (P<0.0001) and consumption of short-acting nitrates was reduced from 3.7±5.6 to 0.7±1.7 units per week (P>0.0001).

**Anti-ischemic efficacy**

Procoralan showed significant anti-ischemic efficacy compared with placebo in the aforementioned randomized, double-blind study reported by Borer et al.20 Procoralan-mediated improvements in time to 1-mm ST segment depression in the double-blind phase were maintained in the open-label phase. Procoralan demonstrated improvements in time to angina onset and time to limiting angina compared with placebo.

In another double-blind, parallel-group, noninferiority trial in 1195 patients with chronic stable angina and documented CAD, Procoralan 7.5 mg bid was associated with substantial antianginal efficacy similar to that of amlopidine 10 mg od, reducing the number of angina attacks by about two thirds and short-acting nitrate consumption by about one half.

The efficacy of Procoralan in reducing the frequency of angina symptoms was also assessed in a 1-year study. Treatment with Procoralan 5 and 7.5 mg bid showed significant reductions in angina attack frequency from 50% to 67% relative to baseline at 1 year of treatment, demonstrating maintenance of antianginal efficacy in long-term therapy, without development of pharmacological tolerance.

A pooled post-hoc analysis of these studies confirmed the antianginal efficacy of Procoralan across a wide range of populations with stable angina, including the elderly, female patients, and patients with asthma/chronic obstructive pulmonary disease. Data from 2425 stable angina patients treated with Procoralan (5, 7.5, or 10 mg bid) for 3 or 4 months demonstrated reduction in frequency of angina attacks by 59.4% and in short-acting nitrate consumption by 53.7, in all subpopulations considered. These data highlight the wide scope of therapeutic usefulness of Procoralan in the management of angina patients.

The antianginal efficacy and safety of Procoralan has also been confirmed in routine day-to-day practice in the large open-label, multicenter REDUCTION trial (not an acronym) conducted in a broad range of patients with stable angina. In this multicenter study, 4954 patients with stable angina pectoris received Procoralan for 4 months. Procoralan angina pectoris attacks decreased from 2.4±3.1 to 0.4±1.3 per week (P<0.0001). Consumption of short-acting nitrates decreased from 3.3±4.4 to 0.6±1.6 units per week (P<0.0001).

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**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<td>ASSOCIATE</td>
<td>Evaluation of the Antianginal efficacy and Safety of the If Inhibitor IvAbradine with a β-Blocker</td>
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<td>BEAUTIFUL</td>
<td>Mortality-Mortality Evaluation of the If Inhibitor IvAbradine in Patients with Coronary Disease and Left Ventricular Dysfunction</td>
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<td>CAD</td>
<td>Coronary Artery Disease</td>
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<td>HR</td>
<td>Heart Rate</td>
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<td>INITIATIVE</td>
<td>International Trial on the Treatment of Angina with IvAbradine vs Atenolol</td>
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<td>LVEF</td>
<td>Left Ventricular Ejection Fraction</td>
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<td>SHIFT</td>
<td>Systolic Heart Failure with the If Inhibitor IvAbradine Trial</td>
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<tr>
<td>SIGNIFY</td>
<td>Study Assessing the Morbidity-Mortality Benefits of the If Inhibitor IvAbradine in Patients with Coronary Artery Disease</td>
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TIATIVE study, an increase in time to 1-mm ST-segment depression by approximately 1.5 min was observed with Procoralan. The Procoralan 7.5 mg bid group showed an increase in total exercise duration, at the trough of drug activity, of 86.8 s, compared with 78.8 s in the atenolol 100 mg od group, and noninferiority was found for all exercise tolerance test parameters (P<0.001) (Figure 2).

The fact that in INITIATIVE there was a similar improvement in exercise capacity with Procoralan for a comparatively smaller reduction in HR suggested greater efficiency in increasing exercise capacity per heartbeat, compared with atenolol. Indeed, for a given reduction of HR (1 beat) Procoralan achieved a greater improvement in exercise capacity (10.1 s) than atenolol (5.6 s). This greater improvement in exercise capacity illustrates the clinical advantage of pure HR reduction, unburdened by effects on other cardiovascular characteristics that limit the heart-rate-reducing benefits.

A recent trial, ASSOCIATE (evaluation of the Antianginal efficacy and Safety of the aSsociation Of the I/ Current Inhibitor ivAbradine with a beTa-blockEr), examined the effects of Procoralan in patients with chronic stable angina pectoris receiving β-blocker therapy. In this double-blind trial in 889 patients, all on 50 mg of atenolol daily, were randomly assigned to additional treatment with either Procoralan up to 7.5 mg bid or a placebo. Patients were then subjected to an exercise treadmill test at trough of drug activity 2 and 4 months later. Findings showed that Procoralan, on top of β-blocker treatment with atenolol, provided further significant long-term improvement in all parameters of the exercise test, at 2 and 4 months (Figure 3). This improvement was consistent across all parameters of the exercise test, at through of drug activity, as evidenced by the rigorous standard Bruce protocol. The most compelling evidence published to date of the benefit of any combination of antianginal drugs. Importantly, despite the fact that combination therapy is widely used in clinical practice to achieve adequate control of angina, clinical trials evaluating combination therapy have yielded inconsistent results. This makes the coadministration of Procoralan with β-blockers the best evidence-based combination therapy for angina patients. ASSOCIATE also showed that treatment was well tolerated, with less than 1% of patients stopping drug therapy because of bradycardia and minor reversible visual effects in 2% of Procoralan-treated patients vs 0.9% of placebo-treated patients. These data establish Procoralan as an effective and well-tolerated anti-anginal agent, alone or in combination with other drugs, including β-blockers.

Figure 2. Anti-ischemic effect of Procoralan in the INITIATIVE trial.
Effect of 4 months of treatment with Procoralan (ivabradine) 7.5 mg bid or atenolol 100 mg od on exercise tolerance parameters at trough of drug activity. P values for noninferiority. INITIATIVE (INternational TRIal on the treatment of angina with ivabradinE vs atenolol). Based on data from reference 21.

Figure 3. Procoralan and exercise tolerance criteria in the ASSOCIATE trial.
Improvement in long-term clinical outcomes in stable CAD patients

In addition to the beneficial effects of HR reduction on the prevention of angina, lower HR is also associated with a more favorable prognosis in patients with CAD. A large body of evidence shows that high resting HR is a strong predictor for cardiovascular mortality and morbidity in patients with cardiovascular diseases.

Procoralan prevents coronary events in CAD patients with elevated HR

The importance of HR as a risk factor and of its reduction for the improvement in prognosis was confirmed in the BEAUTIFUL trial (morbidity–mortality Evaluation of the I1 inhibitor Procoralan in patients with coronary disease and left ventricular dysfunction). This was a large international double-blind randomized clinical trial of Procoralan vs placebo on top of optimal medical therapy in patients with stable CAD and left ventricular dysfunction (left ventricular ejection fraction [LVEF] of less than 40%). A prospective analysis of the data from the placebo arm of BEAUTIFUL evidenced the association of HR with clinical outcomes in this coronary disease population. Patients with a HR of 70 bpm or more had an increased risk of cardiovascular death (34%, \( P=0.0041 \)), admission to hospital for heart failure (53%, \( P<0.0001 \)), admission to hospital for myocardial infarction (46%, \( P=0.0066 \)), and coronary revascularization (38%, \( P=0.037 \)) after adjustment for other predictors of outcome. Consistent with these data on increased cardiovascular risk with HR of 70 bpm or more, Procoralan reduced CAD end points of admission to hospital for fatal or nonfatal myocardial infarction by 36% (\( P=0.001 \)) and coronary revascularization by 30% (\( P=0.016 \)) in these patients at high risk of cardiovascular events (Figure 4). Procoralan also resulted in a 22% reduction in hospitalization for fatal and nonfatal myocardial infarction or unstable angina despite the fact that this population was receiving optimal treatment. Furthermore, there was a 30% reduction in the need for elective revascularization in the whole population with Procoralan vs placebo, most likely because of the well-established effect of Procoralan on anginal pain in patients with stable angina (\( P<0.024 \)).

Procoralan prevents outcomes in symptomatic CAD patients

A recent analysis in 1507 patients with symptoms of angina at baseline in the BEAUTIFUL trial has evaluated the prognostic benefit of Procoralan in this population. The reduction in the primary end point of the study (cardiovascular death, myocardial infarction, or hospitalization for heart failure) was 24% in the whole group of patients with limiting angina and 31% in the group with baseline heart rate \( \geq 70 \) bpm (Figure 5). The primary end point appears to be driven by the coronary outcomes since there was a 42% reduction in the risk for hospitalization for fatal and nonfatal myocardial infarction in patients with limiting angina treated with Procoralan. There were consistent, smaller reductions in all other end points examined, with 13%, 12%, and 28% reductions in all-cause, cardiovascular, and cardiac death, respectively; a 16% reduction in new-onset or worsening heart failure; and a 30% reduction in the risk for coronary revascularization. The reduction in the risk of cardiovascular outcomes was even greater in patients with angina and heart rate \( \geq 70 \) bpm, notably with a significant 73% Procoralan-related reduction in hospitalization for fatal and nonfatal myocardial infarction and a 59% reduction in coronary revascularization. These data confirm that angina places coronary patients at high risk of coronary events. The effect of Procoralan on coronary outcomes is quite remarkable as it extends the efficacy of this agent beyond the symptomatic improvement of anginal or ischemic symptoms.
The results of BEAUTIFUL have important implications, as they showed that elevated heart rate increases cardiovascular risk and should be used to guide optimal therapy in coronary patients. They also evidenced the benefits of Procoralan beyond the control of anginal symptoms. Procoralan is now established as a treatment able to modify the clinical course of CAD and called to play an important role in the management of patients with stable CAD. Another major trial is currently evaluating the efficacy of Procoralan in patients with preserved left ventricular function. This is SIGNIFY (Study assessing the morbidity-mortality benefits of the Iβ blocker ivabradine in patients with coronary artery disease), which will include stable CAD patients with LVEF >40%, and without clinical signs of heart failure. After a run-in period of 2 to 4 weeks, patients will be randomized to placebo bid or Procoralan, with a starting dose of 7.5 mg bid. The target heart rate is 55 to 60 bpm. The study is expected to include more than 16 000 patients from 50 countries.

Clinical benefits of Procoralan in the management of heart failure

The prognostic value of HR in patients with heart failure and the ability of Procoralan to decrease HR without impairing key cardiovascular or hemodynamic parameters such as myocardial contractility, ventricular relaxation, and cardiac conduction, have prompted its evaluation in heart failure. The prevalence of this very disabling condition is rising, due to the aging of the population and the improved survival from conditions such as CAD. Despite advances in the treatment of chronic heart failure (CHF) over the past decade, mortality and morbidity remain high. A number of factors support the benefit that may be derived from HR reduction in heart failure. Elevated HR is associated with impairment of LV filling, decrease in myocardial perfusion, increase in myocardial oxygen consumption, and worsening LV function, and leads to greater mechanical dyssynchrony in patients with CHF. Resting HR is thought to have an independent prognostic value in heart failure, across a large spectrum of severity of the disease.

This concept was successfully tested in the recent SHIFT trial (Systolic Heart failure treatment with the Iβ inhibitor ivabradine Trial). SHIFT was a randomized placebo-controlled clinical trial evaluating the effects of Procoralan, on top of guideline-recommended therapies, on morbidity and mortality in 6558 patients with moderate-to-severe CHF, LV systolic dysfunction (LVEF ≤35%), and resting HR ≥70 bpm. Median follow-up was 22.9 months. More than half of patients were receiving at least 50% of the target dose of β-blocker, with 26% at target dose. Hypotension (44%) and fatigue (32%) were the main reasons for not reaching target dose. After 28 days, Procoralan reduced heart rate by 15.4 bpm (10.9 bpm placebo-corrected). The primary composite end point (CV death or hospital admission for worsening HF) was significantly reduced by 18% (P<0.0001), largely due to significant reductions in death (RRR, 26%; P=0.014) and hospitalization for HF (RRR, 26%; P<0.0001) (Figure 6). Results were consistent across subgroups. On the strength of the absolute risk reduction of the primary end point, 26 patients would need to be treated for 1 year to prevent 1 cardiovascular death or HF-related hospital admission. CV death and all-cause death nominally diminished by 9% and 10%, respectively. Quality of life assessments by both patients and their physicians, as well as New York Heart Association [NYHA] classification, significantly improved with Procoralan. The results of SHIFT clearly demonstrate that Procoralan substantially and significantly reduced major outcomes associated with heart failure when added to guideline-based treatment.

In addition to the clinical standpoint, SHIFT has important implications regarding the pathophysiological standpoint, demonstrating for the first time that HR reduction with Procoralan reduces clinical events in heart failure and therefore that HR is clearly a risk factor in heart failure.
How does Procoralan prevent cardiovascular outcomes?

A growing body of evidence from experimental studies increasingly suggests that pure HR reduction with Procoralan has a significant potential as an intervention able to improve endothelial function and attenuate progression of atherosclerosis, thereby providing cardiovascular protection in addition to the symptomatic treatment of myocardial ischemia. Prevention of endothelial dysfunction, which is the first step in the formation of atherosclerosis, was demonstrated in a transgenic mouse model of dyslipidemia and endothelial dysfunction. Three months’ treatment with Procoralan preserved endothelium-mediated vasodilation in the renal and cerebral arteries of mice expressing human apoprotein B (apoB-100). Procoralan restored the endothelium-dependent vasodilation in cerebral vessels, whereas metoprolol failed to restore endothelial function to the same degree. This could be because of inhibitory effects of metoprolol on β-adrenoreceptor-mediated activation of endothelial nitric oxide synthase.

In addition to improvement in endothelial function, Procoralan also markedly reduced vascular oxidative stress, as reflected by the decrease in NADPH oxidase activity, superoxide production, lipid peroxidation, and monocyte chemotactic protein-1 (MCP-1) expression. MCP-1 provides a link between endothelial dysfunction and atherosclerotic lesion formation by inducing leukocyte arrest and transendothelial migration. Recent experimental data suggest that Procoralan inhibits chemokine-induced migration of CD4-positive lymphocytes, which has a crucial role in early atherogenesis.

All these effects of Procoralan could contribute clinically to the prevention of progression of atherosclerosis. Preclinical studies have shown that Procoralan reduces atherosclerotic plaque size in the aortic root and ascending aorta by 40% and 70%, respectively (P<0.05). All these effects of HR reduction with Procoralan, together with reduced O₂ requirement and improved oxygen supply, could contribute to the clinical benefits of Procoralan reported in the clinical setting.

In a model of CHF, long-term HR reduction with Procoralan improved LV function and increased stroke volume, resulting in preserved cardiac output. This improvement in cardiac function was also associated with modifications of LV structure and/or myocardocyte properties, as indicated by reduction in LV collagen density and increase in LV capillary density.

In parallel with long-term HR reduction, Procoralan significantly reduced plasma norepinephrine levels. In a recently published study in hypercholesterolemic rabbits, Procoralan attenuated LV diastolic dysfunction and reduced atrial fibrosis, ventricular fibrosis, and LV collagen type I. Circulating angiotensin II and aldosterone levels were also reduced with Procoralan and correlated with HR. These beneficial effects on cardiac function and remodeling could also contribute to the beneficial effects of Procoralan in CHF.

These experimental data support the rationale for heart rate reduction with Procoralan as a disease-modifying intervention for improving clinical status and cardiovascular event prevention in patients with CAD or heart failure.

Conclusion

The clinical efficacy and safety of Procoralan in stable angina have been documented in both placebo-controlled and comparative studies, which yielded consistent evidence of the clinical benefits of Procoralan in preventing angina and minimizing underlying ischemia, in monotherapy as well in combination with other treatments, including β-blockers. BEAUTIFUL has shown that, in addition to symptomatic improvement, treatment with Procoralan also improves clinical outcomes in symptomatic coronary patients or those with a baseline HR ≥70 bpm, when added to modern background therapy. The recent SHIFT results have significantly extended the range of clinical benefits of Procoralan by showing substantial reductions in the main heart failure outcomes in patients with CHF. All these findings support the important place of Procoralan as an essential therapeutic modality to improve the management of patients with CAD or heart failure.

References

13. P. Colin, B. Ghaith, X. Monnet, L. Hittinger, A. Berdeaux. Effect of graded heart rate reduction with ivabradine on myocardial oxygen consumption and diss-
Keywords: heart rate reduction; I<sub>C</sub> current; heart failure; ivabradine; stable coronary artery disease
La mortalité cardio-vasculaire est la cause majeure de mortalité prématurée dans la plupart des pays. À côté de l’importance bien établie des facteurs de risque conventionnels, le rôle de la fréquence cardiaque (FC) est maintenant mieux compris comme l’un des déterminants principaux de l’ischémie myocardique et du travail cardiaque. Elle représente de ce fait une opportunité thérapeutique importante, puisqu’elle peut être facilement modifiée en pratique clinique. De grandes études cliniques récentes randomisées ont confirmé les premières données cliniques et épidémiologiques en montrant que la FC au repos est un facteur de risque cardio-vasculaire indépendant chez les patients ayant une maladie coronaire ou une insuffisance cardiaque. La réduction de la fréquence cardiaque est maintenant de plus en plus reconnue comme une approche thérapeutique intéressante chez les patients ayant une maladie coronaire aiguë ou chronique ou une insuffisance cardiaque congestive. Procoralan abaisse la FC de façon sélective, et c’est le premier produit de ce type à être approuvé pour usage thérapeutique. Contrairement aux autres produits abaissant la FC, Procoralan présente un mode d’action original sur l’activité pacemaker du nœud sinusal. Il réduit la FC grâce à son inhibition sélective et spécifique du courant $I_f$, sans aucun effet cardio-vasculaires délétère. Des études cliniques randomisées ont établi le bénéfice clinique de Procoralan dans la prévention de l’angor et la réduction de l’ischémie sous-jacente, en monothérapie comme en association, y compris avec les $\beta$-bloquants. L’étude BEAUTIFUL (morBidity-mortality EvALUaTion of the $I_f$ inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) a montré, chez les patients coronariens stables ayant une dysfonction systolique ventriculaire gauche, en plus de l’amélioration symptomatique, que Procoralan améliorait aussi les résultats cliniques des patients coronariens symptomatiques ou ayant une fréquence cardiaque de base égale ou supérieure à 70 bpm. Les résultats récents de l’étude SHIFT (Systolic Heart Failure treatment with the $I_f$ Inhibitor Ivabradine Trial) ont étendu de façon significative l’ampleur des bénéfices cliniques de Procoralan en montrant des réductions substantielles sur les conséquences de l’insuffisance cardiaque chez les patients atteints d’insuffisance cardiaque chronique. Ceci confirme le rôle essentiel de Procoralan dans l’amélioration de la prise en charge des patients ayant une maladie coronaire ou une insuffisance cardiaque.
Quality of life from the perspective of patients with chronic heart failure

Interview with M. Tendera, Poland

Predictive improvement in patients with heart failure should be paralleled by better quality of life. Therefore, quality of life needs to be taken into account in patient management. Assessment of functional status alone is not adequate, since quality of life is also driven by psychological and social factors. In heart failure patients, not only dyspnea and fatigue, but also depression, have an impact on both quality of life and prognosis. Although quality of life has been mostly measured in the context of clinical trials and surveys, its assessment in clinical practice is feasible and needs to be encouraged. Since impaired quality of life in different diseases have common features, generic tools, such as Euroqual or Short Form (36) (SF-36) Health Survey can be applied in patients with heart failure. The Minnesota Living with Heart Failure (MLHF) questionnaire is the most commonly used specific tool. Different therapeutic strategies, even those shown to improve prognosis, can be associated with side effects perceived by patients as threatening. Patient education plays an important role in alleviating their concerns. Dedicated heart failure clinics, offering continuous counseling and exercise programs, appear to be the best setting to improve self-management and quality of life. In patients with advanced heart failure, the use of devices such as resynchronization therapy and left ventricular support devices, offer both symptomatic and prognostic improvement.

Quality of life (QoL) is not only an important goal of heart failure (HF) treatment, it is also an important measure of the effects of an illness or of a treatment from the patient’s perspective. HF is associated with limitation of physical functioning, withdrawal from activities and social contacts, depression, sleep disturbances, and anxiety, all of which increase with the severity of the disease.

How do major clinical symptoms in heart failure such as dyspnea, tiredness, and fatigue, affect QoL?

Functional impairment, as assessed by the New York Heart Association (NYHA) class, is a very strong predictor of QoL in patients with HF. However, direct comparisons between peak-exertional oxygen consumption and the 6-minute walk test on the one hand, and physical and emotional domains of QoL on the other, showed only mild-to-moderate correlations. Therefore, functional capacity cannot be used as a surrogate of QoL in HF patients.
It needs to be emphasized that emotional distress, as well as social and economic deprivation, also contribute to poor QoL. Limitation in physical capacity experienced by HF patients largely contributes to their loss of status in society and family. Sleep is also an important factor for QoL. Poor sleepers tend to fare less well in physical, psychological, and social domains. In addition, poor health perception and lower education level have been identified as factors that can compromise QoL.

It has to be stressed that patient education, focused on adherence, self-care management, and physical training, can significantly improve QoL. This effect is likely to be accomplished in the setting of the dedicated HF outpatient clinics.

**How is QoL related to other clinical outcomes, such as rehospitalization and mortality rates in heart failure patients?**

Treatment of patients with HF has several goals, most importantly prolongation of survival, alleviation of symptoms, and improvement in QoL. Different therapies may achieve one or more of these goals. There is a clear link between poor QoL and increased risk of hospitalization and death. Psychological distress, especially depression and severe anxiety, are predictors of hospital readmissions in patients with HF.

Recently, worsening of depression was found to be a strong predictor of poor prognosis. Even after controlling for baseline depression and established risk factors, such as HF cause, age, ejection fraction, N-terminal prohormone of brain natriuretic peptide (NT pro-BNP) concentration, and prior hospitalization, depression was associated with poorer prognosis. Therefore, it seems advisable to routinely assess HF patients for depression. The Beck Depressive Inventory is a simple, self-administered tool that can be used for this purpose.

**Could you talk to us about the generic and disease-specific tools used to assess patient QoL in heart failure surveys and studies?**

Generic tests are useful because impairment of QoL is only partly dependent on the nature of the disease. A recent study comparing patients with advanced cancer, chronic obstructive pulmonary disease (COPD), and HF found that the physical and psychological burdens of the disease show many similarities.

There are a number of different generic tests that can be used to assess health-related QoL in patients with HF. They range from simple questions assessing overall patient well-being at a certain point in time or comparing it with the previous status, to more complex questionnaires addressing different dimensions of QoL. The Euroqual scale represents a calibrated 100-mm line, on which 0 corresponds to the worst, and 100 to the best overall feeling at the time of assessment. The MacMaster Overall Treatment Evaluation (OTE) questionnaire represents a different approach. It does not provide overall assessment of well-being, but gives a comparison of the current status with the previous one, based on no change, or different degrees of improvement or worsening. These simple generic tests address the general perceived health status rather than the whole spectrum of QoL.

In contrast, the 36-item Short Form (SF-36) Health Survey was designed to assess eight health domains: limitations in physical, usual role, and social activities, bodily pain, psychological distress, vitality, and general health perception. SF-36 is self-administered, its validated form is available in many different languages, and it can be used in clinical practice and research, as well as in general population surveys, in patients with various health problems.

The Minnesota Living with Heart Failure (MLHF) questionnaire was specifically designed for use in HF patients. It consists of 21 questions. The answers are numerical, ranging from 0 to 5, with 0 denoting no impact, and 5 a serious impact of HF. The questions address the physical dimension, most importantly the impact of muscle fatigue and dyspnea, and the emotional dimension of QoL. The MLHF questionnaire proved to be useful in clinical research to quantify the effect of different interventions, such as drug treatment, resynchronization therapy, exercise programs or multidisciplinary HF units on the well-being of patients with HF.

Both generic (SF-36) and disease-specific (MLHF) tools proved useful in predicting long-term mortality in patients with HF. A poor mental component score in SF-36, and physical component summary in MLHF were associated with an increase in all-cause mortality (hazard ratio 1.38 and 1.31, respectively).

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item, self-administered questionnaire with scales quantifying multiple domains of health status for patients with heart failure, including symptoms, physical function, social function,
self-efficacy, and health-related quality of life. Each scale is scored from 0 to 100, where a higher score represents better health status. To facilitate interpretability, two summary scores were developed: Overall Summary Score (OSS) and Clinical Summary Score (CSS). The validity, reproducibility, and sensitivity to clinical change of the KCCQ have been well established in populations with heart failure.²

It is important to remember that QoL assessment needs to be done at the very beginning of the patient’s visit, before the contact with the managing physician, in order to avoid bias related to the patient-doctor interaction.

**How should a patient be approached in clinical practice to assess QoL?**

Patients’ well-being is always addressed by physicians, who most commonly open the conversation by asking “How are you feeling?” However, formal assessment of QoL is rarely used in clinical practice. QoL is usually substituted by symptomatic improvement, which only reflects the physical component of QoL. It is, however, clear that QoL can be easily and successfully assessed outside of clinical research.¹⁰ Moreover, nonphysical domains of QoL, such as depression, can have an important impact not only on patients’ well-being, but also on prognosis.³ Therefore, QoL should be more commonly assessed in clinical practice, in order to recognize and better address different patients’ needs. All the tools, both generic and disease specific, are simple enough to administer in clinical practice. Time constraints related to everyday patient care may be a limiting factor in formal QoL assessment implementation.

**To what extent do side effects of treatment adversely affect QoL and lead to poor compliance with treatment in heart failure patients?**

Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and β-blockers have a well-documented positive effect on survival in patients with HF. ACE inhibitors and ARBs improve exercise tolerance and thereby positively influence QoL. The effects of β-blockers are more complex.

The meta-analysis assessing the impact of β-blocker therapy on quality of life in HF patients in a total of 9 trials involving 1954 patients found only a trend toward improvement in QoL in HF patients receiving β-blockers, but the effect was very small and did not reach statistical significance.¹¹ Mortality reduction is dose dependent, but dose increase may aggravate side effects, such as bradycardia, hypotension, fatigue, sleep disorders, cold extremities, or sexual dysfunction, which may impair QoL. On the other hand, diuretics or digitalis may improve QoL, while having either a neutral or a negative effect on survival.

Patients who experience drug-related adverse events often perceive them as serious (46%), with major consequences on their daily life (40%).¹² All known side effects of treatment need to be discussed with the patients up front, in order to make them understand their nature and avoid an unnecessary negative impact on QoL.

Occurrence of side effects does not always necessitate treatment termination. In those instances where treatment should and can be continued, worsening in QoL may be a price to pay for a chance of improved survival. The patient’s informed decision is crucial here, to avoid treatment compliance being affected.

**How important is QoL in the clinical decision-making process and when determining therapeutic benefits?**

Without doubt, a parallel improvement in prognosis and QoL is the best case scenario. As mentioned earlier, treatment with ACE inhibitors, ARBs, and β-blockers is usually associated with improved prognosis and better QoL, while β-blockers showed a neutral effect on QoL. Combination of isosorbide dinitrate and hydralazine in African-American patients with HF is also associated with a positive prognostic effect and improvement in QoL.

Recent data indicate that both prognostic and functional improvement may be achieved in patients with advanced HF with the use of left ventricular assist devices (LVAD).¹³ Despite high costs, a substantial growth of the number of implanted LVAD, especially those with continuous flow, has been observed in the US in recent years.¹⁴ Since the European Society of Cardiology clinical practice guidelines for the first time accepted LVAD as destination therapy in advanced HF, the same trend may be expected in Europe.

Most of the time, prognostic improvement should be the ultimate goal of treatment. It should be mentioned, however, that improved QoL may be preferred over life prolongation by certain patient subsets, such as the very elderly and those with terminal disease. Poor QoL affects not only the patients, but also people who care for them. Thus, an open discussion of the preferences with the patients and their families is extremely important. Assisting HF patients in maintaining a positive attitude toward their health status should be an important treatment goal.

**How important is assessment of QoL in clinical trials for interpreting clinical outcomes? Is it complementary to other end points?**

It is very important, and most outcome trials conducted in HF patients do take QoL into account. Mortality and morbidity parameters are easy to measure, and their statistical
analysis helps in establishing treatment efficacy and safety in the studied cohort. Statistics, however, do not reflect the situation of an individual patient enrolled in the study who perceives medical events on a binary basis (yes or no). It is therefore of crucial importance to study patients’ perception of health-related limitations in different domains of their life. Formal assessment of QoL serves this purpose. The patient is a subject, not an object of treatment. It is therefore crucial to explore his/her point of view on monitoring medical care outcomes.

References

Keywords: heart failure; quality of life; questionnaire; self-management; side effect

QUALITÉ DE VIE DU POINT DE VUE DES PATIENTS ATTEINTS D’INSUFFISANCE CARDIAQUE CHRONIQUE

L’amélioration du pronostic des patients atteints d’insuffisance cardiaque devrait concorder avec une meilleure qualité de vie. Celle-ci doit donc être prise en compte dans le traitement du patient. L’évaluation du statut fonctionnel seul n’est pas pertinente, puisque la qualité de vie est aussi dépendante de facteurs psychologiques et sociaux. Chez les patients insuffisants cardiaques, dyspnée et fatigue, mais aussi dépression, ont un impact à la fois sur la qualité de vie et sur le pronostic. Si la qualité de vie est habituellement mesurée dans le contexte des études et des enquêtes cliniques, son évaluation en pratique clinique est possible et doit être encouragée. L’altération de la qualité de vie ayant, dans différentes pathologies, des caractéristiques communes, des outils génériques comme l’Euroqol ou le SF-36, Short Form (36), peuvent s’appliquer chez les patients insuffisants cardiaques. Le questionnaire MLHF (Minnesota Living with Heart Failure) est l’outil spécifique le plus couramment utilisé. Différentes stratégies thérapeutiques, même celles qui améliorent le pronostic, peuvent entraîner des effets indésirables perçus par les patients comme menaçants. L’éducation du patient joue un rôle important pour remédier à ces problèmes. Des services hospitaliers dédiés à l’insuffisance cardiaque, offrant des programmes d’exercice et d’assistance continus, semblent fournir le meilleur cadre pour améliorer l’auto-surveillance et la qualité de vie des patients. Quant aux patients souffrant d’une insuffisance cardiaque avancée, l’utilisation d’outils comme le traitement par resynchronisation et les dispositifs d’assistance ventriculaire gauche fournit une amélioration à la fois symptomatique et pronostique.
Heart rate regulates cardiovascular output during stress and exercise. Chronic elevated heart rate is associated with increased morbidity and mortality in the general population at risk and in patients with cardiovascular disease. Physiological studies have shown that a high resting heart rate induces endothelial dysfunction, predisposes plaque to rupture, and is associated with cardiovascular end points like myocardial infarction and heart failure. High heart rates produce endothelial dysfunction through alteration of shear stress, and also accelerate atherosclerosis. Furthermore, elevated heart rate reduces the energy supply of the heart by reducing the length of diastole and increasing oxygen consumption. In heart failure, cardiac output is reduced through an inversion of the positive Treppe phenomenon (Bowditch effect). Heart rate is now regarded not only as a risk indicator, but a risk factor, because heart rate reduction has been shown to reduce cardiovascular events in patients with chronic heart failure. Meanwhile, clinical studies have provided pathophysiological proof for concepts that were generated through experimental investigation and observational and epidemiological studies.

The SHIFT trial produced the first evidence that selective heart rate reduction with no other myocardial effects, as provided by ivabradine, has beneficial effects in heart failure patients with reduced left ventricular ejection fraction (LVEF). The improvement reported in a case study of a patient with heart failure with preserved ejection fraction (HFPEF) leads to speculation that ivabradine might produce results superior to those of β-blockers in this special hemodynamic setting.”

Elevation of heart rate usually occurs as an adaptation of the cardiovascular system to increased demand from the peripheral circulation. Heart rate is regulated by the sympathetic and parasympathetic nervous systems and reflects important parameters in health and disease. Heart rate is a major determinant of myocardial oxygen demand, coronary blood flow, and myocardial performance, and has an effect at nearly all stages of cardiovascular disease.1,2 Many studies have focused on the predictive value of heart rate for cardiovascular outcomes in both the general population and individuals affected by cardiovascular diseases.3 Data show that elevated resting heart rate is an indicator of cardiovascular risk independent of currently accepted risk factors and other potentially confounding demographic and physiological characteristics,4,5 and that it is an important predictor of mortality in patients with coronary artery disease, myocardial infarction, and chronic heart failure.6-10 Experimental and clinical evidence suggests that sustained elevation in heart rate—irrespective of the underlying trigger—plays a direct and causal role in the pathogenesis of atherosclerosis and myocardial injuries, affects initiation and progression as well as severity of the disease, and contributes to precipitation of vascular and myocardial events.11
Atherosclerosis and myocardial infarction

Many studies have shown that an increase in heart rate is associated with an increase in stiffness of vessels, in particular the aorta. In vascular muscle cells, it was found that there is an increase in collagen production after stretching. This effect was dependent on the rate and amplitude of stretch. Accordingly, in primates with tachycardic pacing, there was decreased compliance of the carotid arteries. Consistently, in patients who died after an acute myocardial infarction, it was shown that the extent of coronary atherosclerosis was closely related to (higher) heart rate. In primates, ablation of the sinus node was associated with a reduction in cholesterol-induced atherosclerosis. Consistent with this finding, in Apo-E knockout mice, it was observed that cholesterol-induced atherosclerosis could be reversed by 70% when rate heart was decreased by 10% using the If channel inhibitor ivabradine. In addition, ivabradine was able to improve endothelial function in early forms of cholesterol-induced atherosclerosis. Improvement in endothelial function was associated with a reduction in free radicals. As shear stress during diastole is important for maintenance of endothelial function, it was speculated that reduction in shear stress during diastole could induce endothelial dysfunction and increase free radical formation in the vessel wall, and that this could be a target for treatment with a heart rate-reducing agent like the If channel blocker ivabradine.

These pathophysiological findings are in line with the clinical and epidemiological findings. The long-term prognosis of patients with stable coronary artery disease was found to be dependent on resting heart rate. In another study of 24,913 patients, it was found that total mortality rate, cardiovascular disease mortality rate, and the rate of cardiovascular rehospitalization increased with increasing heart rate. Patients with resting heart rate of more than 83 beats per minute (bpm) had an increased overall relative risk of 1.24 and an elevated cardiovascular mortality risk of 1.31 compared with controls. Myocardial infarction develops when coronary plaques rupture and thrombosis occludes the vessel. Accordingly, the significance of heart rate regarding prognosis after myocardial infarction has also been shown; patients with myocardial infarction had significantly elevated heart rates compared with controls. Furthermore, higher heart rates at hospital discharge correlated with an increased mortality rate after 1 year. Meta-analyses of the Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto miocardico (GISSI)-2 and GISSI-3 trials, which included about 20,000 patients, demonstrated that the in-hospital mortality rate in patients post–myocardial infarction rose from 3.3% for those with admission heart rates of <60 bpm to 10.1% for those with heart rates >100 bpm on admission. The relevance of heart rate after myocardial

Figure 1. Effect of heart rate (bpm, beats per minute) on mortality in patients with myocardial infarction.

Figure 2. Aortic atherosclerosis in Apo-E knockout mice treated with vehicle or ivabradine. Staining of aortic plaque in the aortic sinus (upper panels) and ascending aorta (lower panels), and quantification of plaque load (far right). A 10% reduction in heart rate is associated with a 50% to 75% reduction in plaque load.
Infarction is supported by results from β-blocker trials. Heart rate reduction with β-blockers is associated with a decrease in total mortality and sudden cardiac death. In addition, heart rate–reducing verapamil-like calcium antagonists have been shown to exhibit beneficial effects on the prognosis of patients after myocardial infarction in the absence of heart failure.

Results of the important first morbidity and mortality trial investigating pure heart rate reduction in coronary heart disease were recently published by the BEAUTIFUL investigators (morBidity-mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary artery disease and left ventricular dysfunction). This international multicenter trial was a randomized, double-blind, placebo-controlled investigation, and enrolled 10,917 patients with coronary artery disease and left ventricular dysfunction (left ventricular ejection fraction (LVEF) <40%). The aim of the study was to investigate whether heart rate reduction with ivabradine reduces cardiovascular death and morbidity in these patients. The active treatment group was treated with 5 mg twice daily of ivabradine, with a target dose of 7.5 mg twice daily. All patients continued their high-level therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (90%), as well as β-blockers (87%). The mean heart rate at entry was rather low (71.6 bpm) and the corresponding mean LVEF (32.4%) was significantly depressed. The primary end point comprised a composite of cardiovascular death, admission to hospital for acute myocardial infarction, admission to hospital for new onset or worsening of heart failure, and revascularization. The aforementioned clinical and epidemiological data provide proof of concept that the pathophysiological finding of a high heart rate is of clinical relevance to the structure and function of the vascular cell.

Heart failure

Elevated heart rate at rest is one of the key findings in acute and chronic heart failure. Chronic heart failure is associated with maladaptive neuroendocrine activation processes, which involve an elevation of resting and exercise heart rates. Pathophysiologically, in failing human myocardium, there is an inverse of the so-called Treppe phenomenon (Bowditch effect), which results in reduced contractility when heart rate is increased. In addition to the reduction of developed force, diastolic function is also reduced at elevated heart rates (Figure 3).

Large-scale randomized controlled morbidity and mortality studies have been performed in patients with heart failure with reduced ejection fraction with β-blockers, ACE inhibitors, angiotensin receptor blockers, and aldosterone antagonists. All studies have demonstrated a significant reduction in both mortality and morbidity (up to 30%) with the investigated agent. β-Blockers on top of standard therapy was generally regarded to be necessary.
Heart rate reduction in heart failure: pathophysiological perspectives – Böhm and others

Heart failure with preserved ejection fraction (HFPEF) is characterized by concentric left ventricular hypertrophy with impaired relaxation and reduced compliance, accompanied by only mildly impaired ejection fraction of ≥50%. Survival rates in patients with HFPEF have remained largely unchanged over the last two decades. Currently, only symptomatic treatment is given. Apart from the prescription of diuretics for HFPEF patients with pulmonary congestion and edema, the therapeutic goals are treatment of hypertension and myocardial ischemia, maintenance of sinus rhythm, optimal treatment of diabetes mellitus, and heart rate control. In addition to reducing afterload, heart rate reduction prolongs diastole and left ventricular filling time, providing additional time for diastolic relaxation due to improved Ca²⁺ ion reuptake into the sarcoplasmic reticulum. Consequently, lower heart rate reduces pulmonary pressure and extends diastolic coronary perfusion time, thereby preventing ischemia-induced diastolic dysfunction.

Unloading of the left ventricle with heart rate reduction was elegantly demonstrated in a case study of a patient with HFPEF (Figure 5, page 448). In the upper panel, left ventricular and pulmonary artery pressure curves are depicted at high heart rate (119 bpm). After an injection of 5 mg metoprolol, the heart rate decreases (to 96 bpm) at nearly constant systemic pressure (aorta), while the pressure of the pulmonary artery considerably declines (lower panel). These findings demonstrate that in this patient with HFPEF, improvement of left ventricular diastolic filling is associated with a decrease in pulmonary pressure. At present, one can only speculate as to whether pure heart rate reduction with ivabradine could produce results even superior to those of β-blockers in this special hemodynamic setting. Currently, however, there are no head-to-head trials comparing pure heart rate reduction with β-blockers in HFPEF patients with pulmonary congestion and edema. In the SHIFT trial, ivabradine reduced heart rate by 11 bpm from an average baseline heart rate of 80 bpm. Heart rate reduction with ivabradine reduced the primary composite end point of cardiovascular death and hospitalization for heart failure significantly (20% reduction with ivabradine vs. placebo, P<0.001). The benefit was independent of baseline heart rate and was evident in patients with lower and higher baseline heart rates (>80 bpm), as well as with markedly reduced heart rates after drug treatment (>10 bpm reduction). It is currently unknown, however, as to whether or to what extent—the benefit of β-blockers for patients with heart failure is due to heart rate reduction per se, or other beneficial effects derived from interrupting maladaptive β-signaling pathways (apoptosis, fetal gene expression, Ca²⁺ handling, etc.). As β-blockers considerably reduce heart rate (negative chronotropy), they are most appropriate for comparison with ivabradine, a recently designed drug that delivers pure heart rate reduction through I førin channel inhibition.

The first evidence providing proof of concept regarding the role of heart rate in heart failure came from Systolic Heart failure treatment with the I før inhibitor ivabradine Trial (SHIFT). SHIFT investigated the effect of selective heart rate reduction with ivabradine on top of proven recommended therapies in heart failure patients with a heart rate of >70 bpm in sinus rhythm and an LVEF of <35%. This controlled trial randomized 6500 patients with stable symptomatic heart failure (New York Heart Association II–IV) to ivabradine (target dose 7.5 mg twice daily) or placebo. Patients were intensively treated with recommended therapies (ACE inhibitors or angiotensin receptor blockers [92%], β-blockers [90%]). Ivabradine reduced heart rate by 11 bpm from an average baseline heart rate of 80 bpm. Heart rate reduction with ivabradine reduced the primary composite end point of cardiovascular death and hospitalization for worsening heart failure by 18%. Patient risk was closely dependent on baseline heart rate. Patients with a heart rate of <60 bpm on treatment with ivabradine had the lowest risk, while the risk doubled in patients remaining at a heart rate >80 bpm. A 5-bpm higher resting heart rate at increased the risk by 15% each year for cardiovascular death and heart failure hospitalization (Figure 4). SHIFT produced the first evidence that selective heart rate reduction with no other myocardial effects, as provided by ivabradine, has beneficial effects in patients with reduced ejection fraction.

The significance of heart rate on mortality was retrospectively addressed in subanalyses of the Cardiac Insufficiency Bisoprolol Study–II (CIBIS-II), MEtoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure (MERIT-HF), and Carvedilol Or Metoprolol European Trial (COMET). These large studies together enrolled a total of almost 10 000 patients with advanced systolic heart failure (New York Heart Association class II–IV). The general trend from these three trials clearly demonstrates that high heart rate at rest contributes to poor survival. These results are in line with those from previous studies of β-blockers and other drugs approved for heart failure therapy demonstrating greater benefits with higher baseline heart rates (>80 bpm), as well as with markedly reduced heart rates after drug treatment (>10 bpm reduction). It is currently unknown, however, as to whether or to what extent—the benefit of β-blockers for patients with heart failure is due to heart rate reduction per se, or other beneficial effects derived from interrupting maladaptive β-signaling pathways (apoptosis, fetal gene expression, Ca²⁺ handling, etc.). As β-blockers considerably reduce heart rate (negative chronotropy), they are most appropriate for comparison with ivabradine, a recently designed drug that delivers pure heart rate reduction through I førin channel inhibition.

Figure 4. Cardiovascular outcome in patients with stable heart failure (NYHA class II–IV) treated with ivabradine according to heart rate achieved at day 28 after uptitration. Abbreviations: NYHA, New York Heart Association; bpm, beats per minute. After reference 39: Boehm et al. Lancet. 2010;376:886-894. © 2010, Elsevier Ltd.
Focus

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no data available in HFPEF patients on the use of specific heart rate–reducing agents. Studies of this condition evaluating the pathophysiology and practical clinical benefits of such therapies are highly warranted. Case reports dealing with special hemodynamic alterations in cardiovascular disease, in particular heart failure, can demonstrate individual experiences with ivabradine.41 One patient with heart failure with reduced ejection fraction and acute left ventricular decompensation developed sinus tachycardia (120 bpm) with dyspnea while under dobutamine infusion on a cardiac care unit. Ivabradine was subsequently carefully titrated orally up to a dose of 15 mg/day to reduce heart rate while the patient was still undergoing dobutamine therapy. Within 5 days, heart rate had decreased (–34%) and there was a striking increase in stroke volume (+40%) accompanied by a simultaneous decrease in systemic and pulmonary vascular resistance (Figure 6). After ivabradine withdrawal, hemodynamic values worsened again, but readministration of ivabradine led to a weaning from dobutamine therapy over the next 3 days, and the patient recovered. This report and previous studies demonstrate the beneficial hemodynamic effects of ivabradine, even in acute hemodynamic deterioration.42

Figure 5. Hemodynamic effects induced by heart rate reduction in a patient with heart failure with preserved ejection fraction.

Upper panel: Left ventricular pressure (red pressure curve) and pulmonary artery pressure (white pressure curve) at high heart rate (120 bpm). Lower panel: after intravenous administration of 5 mg metoprolol, heart rate is reduced (96 bpm). As a result, the mean pressure of the pulmonary artery considerably declines (from 46 mm Hg to 27 mm Hg), while systemic pressure (aorta) remains virtually unchanged.

Abbreviations: DP, diastolic pressure; EDP, end diastolic pressure; LV, left ventricular; HR, heart rate; MP, mean pressure; SP, systolic pressure.


Figure 6. Hemodynamic improvement on ivabradine during acute left ventricular decompensation in advanced heart failure.

Ivabradine was titrated, withdrawn (0 mg/day), and readministered in order to wean the patient from dobutamine infusion (9 µg/kg/min).

Abbreviations: BPM, beats per minute; HR, heart rate; PVR, pulmonary vascular resistance; SV, stroke volume; SVR, systemic vascular resistance.

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Conclusion
Clinical and experimental studies support a significant association between elevated heart rate and a broad range of maladaptive vascular and myocardial effects. Increased heart rate impairs endothelial function in animal models, and may contribute to reduced vascular function. Heart rate reduction inhibits formation of atherosclerotic plaque in animal models of lipid-induced atherosclerosis, and may prevent or retard the final development in chronic heart failure. While experimental, epidemiological, and observational data have attracted interest, studies like BEAUTIFUL and SHIFT have provided considerable proof of the pathophysiological concept. The major task is to broaden this concept to conditions like heart failure with preserved ejection fraction, for which there are currently no treatments available proven to have an effect on clinical end points.

References
RÉDUCTION DE LA FRÉQUENCE CARDIAQUE DANS L’INSUFFISANCE CARDIAQUE : PERSPECTIVES PHYSIOPATHOLOGIQUES

La fréquence cardiaque contrôle le débit cardiaque au cours du stress et de l’effort. L’élévation chronique de la fréquence cardiaque entraîne une augmentation de la morbidité et de la mortalité dans la population générale à risque et chez les patients atteints de pathologie cardio-vasculaire. Des études physiologiques ont montré qu’une fréquence cardiaque de repos élevée induit une dysfonction endothéliale, prédispose à la rupture de plaques d’athérosclérose et s’associe à des événements cardio-vasculaires tels que infarctus du myocarde et insuffisance cardiaque. Une fréquence cardiaque élevée engendre une dysfonction endothéliale par l’intermédiaire d’une altération de la contrainte de cisaillement et accélère également l’athérosclérose. De plus, une fréquence cardiaque élevée réduit les apports énergétiques du cœur en diminuant la longueur de la diastole et en augmentant la consommation d’oxygène. Dans l’insuffisance cardiaque, le débit cardiaque est réduit par une inversion de l’effet escalier positif dit « effet treppe » ou effet de Bowditch. La fréquence cardiaque est maintenant considérée non seulement comme un indicateur de risque, mais comme un facteur de risque, sa réduction diminuant les événements cardio-vasculaires chez les patients atteints d’insuffisance cardiaque chronique. Des études cliniques ont apporté une confirmation physiopathologique à ces concepts issus de la recherche expérimentale et d’études observationnelles et épidémiologiques.

Keywords: cardiovascular disease; heart failure; heart rate; pathophysiology; risk factor; ivabradine
The new ESC Guidelines set new standards of clinical excellence and their implementation is expected to have a major impact in clinical practice in reducing the complications of heart failure. The ESC has as a strategic priority, not only the production of high-quality guidelines, but also their correct implementation. What is needed is systematic and organized collaboration between national societies and the ESC and an assessment of the results on an annual basis.

What are the new ESC guidelines on device therapy in heart failure?

by P. E. Vardas, Greece

New data derived from recent clinical trials necessitate the update of the previous 2008 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure and the 2007 ESC Guidelines for Cardiac Pacing and Resynchronization Therapy. The 2010 Focused Update of ESC Guidelines on Device Therapy in Heart Failure was developed by a Task Force of 10 European experts in heart failure and cardiac resynchronization therapy, with the special contribution of the Heart Failure Association (HFA) and the European Heart Rhythm Association (EHRA). The new Guidelines represent a comprehensive document, which concerns not only cardiologists, but all physicians interested in the field. There are a number of important main features that distinguish this Guidelines document from its predecessors. This article briefly highlights the main messages derived from the new 2010 Focused Update of ESC Guidelines on Device Therapy in Heart Failure. The new Guidelines set new standards of clinical excellence and their implementation is expected to have a major impact in clinical practice in reducing the complications of heart failure.

Medicographia. 2011;33:451-456 (see French abstract on page 456)

In contrast to previous guidelines, this focused update considers the characteristics of the patients included in the trials and contains several examples. In MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy), only 15% of the patients were classified as New York Heart Association [NYHA] class I, although the protocol permitted inclusion of patients in both NYHA I and II functional class and the favorable effect on the primary endpoint was limited to patients with a QRS width ≥150 ms, although the inclusion criteria permitted randomization of patients with a QRS width ≥130 ms.
This article briefly highlights the changes from the prior guidelines and the main messages derived from the new 2010 Focused Update of ESC Guidelines on Device Therapy in Heart Failure.

**Synopsis of the previous guidelines for cardiac resynchronization therapy**

The previous ESC/EHRA 2007 Guidelines for Cardiac Pacing and Cardiac Resynchronization Therapy recommended the use of cardiac resynchronization therapy by pacemakers (CRT-P) or implantable cardioverter defibrillator (ICD) devices (CRT-D) in HF patients, who remain symptomatic in New York Heart Association (NYHA) classes III-IV, despite optimal medical therapy, with:
- Left ventricular ejection fraction (LVEF) ≤35%.
- Left ventricular (LV) dilatation.
- QRS complex ≥120 ms.
- Normal sinus rhythm.

That was a Class I, Level of evidence A recommendation for CRT-P to reduce morbidity and mortality, and CRT-D was an acceptable option for patients who had a survival expectancy of >1 year.

Table I summarizes the class and the level of evidence of the recommendations for CRT for specific issues mentioned in the previous 2007 pacing guidelines.

**New guidelines for CRT-P/CRT-D in patients with heart failure in NYHA class III/IV**

A large number of randomized multicenter trials with crossover or parallel treatment design using CRT pacemakers (CRT-P) or CRT-ICD devices (CRT-D) have evaluated the long-term clinical effects of CRT. The usual study enrollment criteria were: NYHA functional class III or IV despite optimal pharmacological treatment, LVEF ≤35%, sinus rhythm, LV dilatation, and QRS duration ≥120/≤130 ms. Meta-analyses also suggested that the most efficacious option in patients with HF and low LVEF would be a CRT-D. The aforementioned randomized clinical trials confirmed a significant alleviation of symptoms and exercise capacity conferred by CRT.

In order to keep these guidelines up to date, the new guidelines modify the recommendations and levels of evidence according to the most recent clinical trial evidence as follows.

**Selected Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AF</td>
<td>atrial fibrillation</td>
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<td>AV</td>
<td>atrioventricular</td>
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<td>CARE-HF</td>
<td>Cardiac RESynchronization–Heart Failure [trial]</td>
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<td>COMPANION</td>
<td>Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure [trial]</td>
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<td>CRT-D</td>
<td>cardiac resynchronization therapy/defibrillators</td>
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<tr>
<td>CRT-P</td>
<td>cardiac resynchronization therapy/pacemakers</td>
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<td>EHRA</td>
<td>European Heart Rhythm Association</td>
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<td>ESC</td>
<td>European Society of Cardiology</td>
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<td>HF</td>
<td>heart failure</td>
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<tr>
<td>ICD</td>
<td>implantable cardioverter defibrillator</td>
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<td>INTERMACS</td>
<td>Interagency Registry for Mechanically Assisted Circulatory Support</td>
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<td>LBBB</td>
<td>left bundle-branch block</td>
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<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
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<td>MADIT-CRT</td>
<td>Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy</td>
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<tr>
<td>MIRACLE ICD</td>
<td>Multicenter, InSync™ RAndomized CLinical Evaluation Implantable Cardioverter Defibrillator</td>
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<tr>
<td>RAFT</td>
<td>Resynchronization/defibrillation for Ambulatory Heart Failure Trial</td>
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<tr>
<td>RBBB</td>
<td>right bundle-branch block</td>
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<tr>
<td>REVERSE</td>
<td>Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction [trial]</td>
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In COMPANION, CRT-D was associated with a significant decrease in all-cause mortality (relative risk reduction: 36%; *P*=0.003), while the 24% relative risk reduction in mortality associated with CRT-P was nearly statistically significant (*P*=0.059).

In CARE-HF, CRT-P produced a 36% relative reduction in the risk of death (*P*<0.002) after a mean follow-up time of 29 months. In the CARE-HF extension study, a relative risk reduction of 40% (*P*<0.0001) was observed, mainly due to a marked reduction in HF-related deaths. Moreover, a consistent finding in the randomized trials has been an absolute re-

**Table I. CRT for specific issues mentioned in the previous 2007 pacing guidelines.**

**Abbreviations:** CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter defibrillator.
duction in LV end-diastolic diameter and an increase in LVEF following CRT. In the CARE-HF study, the mean reduction in LV end-systolic volume was 18% at 3 months and 26% after 18 months of CRT. Similarly, the mean LVEF increase was 3.7% at 3 months increasing to 6.9% at 18 months.

These findings provided strong evidence of a sustained and progressive reverse remodeling effect conferred by CRT. The effect was significantly greater in patients with nonischemic than in those with ischemic heart disease. Regarding QRS morphology (left bundle-branch block, LBBB vs right bundle-branch block, RBBB), a baseline typical LBBB pattern predicted a favorable outcome defined as freedom from death or major cardiovascular event in the CARE-HF study.

As a consequence of the results of the aforementioned studies, the new guidelines recommend the use of CRT-P/CRT-D to reduce morbidity and mortality (Class I, level of evidence A) in patients with NYHA function class III/IV, LVEF ≤35%, QRS ≥120 ms, sinus rhythm, and optimal medical therapy. It is also stated that reasonable expectation of survival with good functional status for >1 year is required for CRT-D and that patients with a secondary prevention indication for an ICD should receive a CRT-D.

Regarding class IV patients, it is clearly stated that they should be ambulatory: no admissions for HF during the last month and a reasonable expectation of survival >6 months. Comparing the new recommendations with the previous ones, the reader will discover that LV dilatation is no longer required in the recommendation, class IV patients should be ambulatory, and a reasonable expectation of survival with good functional status for >1 year is required for CRT-D implantation. It is also specified that the level of evidence is similar for CRT-P and CRT-and strongest for patients with typical LBBB.

New guidelines for CRT-D in patients with heart failure in NYHA class II/III

As already mentioned, CRT was not recommended in the 2007 guidelines, in patients with mild HF or asymptomatic LV systolic dysfunction (Class III, Level of evidence C).

The clinical impact of CRT in mildly symptomatic or asymptomatic patients with a depressed LVEF and a wide QRS complex has been evaluated in three trials:

- **MIRACLE ICD II** (Multicenter, InSync™ RAnomized ClInical Evaluation Implantable Cardiöverter Defibrillator II) was a small pioneer trial that enrolled 186 candidates for ICD, who presented with NYHA function class II and sinus rhythm, and whose LVEF was ≤35%, QRS duration ≥130 ms, and LV end-diastolic diameter ≥55 mm. All patients received a CRT-D, and CRT was randomly activated in 85 patients. Despite the development of significant reverse LV remodeling, their exercise capacity was not increased.

- MADIT-CRT enrolled 1820 patients in NYHA function classes I (15%) of ischemic etiology or II (84%) of any etiology and sinus rhythm, whose LVEF was ≤30% and QRS duration ≥130 ms. Using a 2:3 randomization scheme, 731 patients were assigned to receive an ICD and 1089 received a CRT-D. The primary end point was a composite of death from any cause and nonfatal HF-related adverse events. During a mean follow up of 2.4 years, the relative risk of sustaining a primary end point was reduced by 34% in the CRT-D-treated group, a benefit attributable primarily to a 41% decrease in HF-related adverse events. However, there was no significant difference in mortality between the CRT-D- and ICD-only arms.

- The REVERSE trial (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) enrolled 610 NYHA class II patients and class I patients with previous HF symptoms, with QRS ≥120 ms, EF <40%, and LV end-diastolic diameter ≥55 mm. They underwent implantation of a CRT-D or CRT-P, according to the investigators’ recommendations, though, ultimately, only 15% of patients received a CRT-P. Patients were randomly assigned to CRT activated (ON) versus CRT not activated (OFF). The primary end point was the HF clinical composite response that scored patients as improved, unchanged, or worsened over a relatively short follow-up of 12 months. The study did not meet the primary end point: 16% of patients worsened in the CRT-ON compared with 21% in the CRT-OFF (P=0.10) group. However, patients assigned to CRT-ON experienced a greater improvement in LV end-diastolic volume index and other measures of LV remodeling. European investigators of this trial followed 262 of the patients up to 24 months and the primary end point of worsening was found to be significantly lower in the CRT-ON group than in the CRT-OFF group (19% vs 34%, respectively; P=0.01). Time to first HF hospital stay or death in the European cohort was also significantly delayed by CRT.

We should also mention that in prespecified subgroup analyses of data collected in MADIT-CRT and REVERSE, patients with a wide QRS duration ≥150 ms, as well as female patients, had significantly more benefit from CRT-D than male patients with QRS <150 ms. Further analyses revealed that patients with LBBB derived a significant benefit from CRT-D, whereas patients with a wide QRS complex and RBBB or indeterminate ventricular conduction disturbances (regardless of QRS duration) did not demonstrate reduction in primary events.

MADIT-CRT and REVERSE enrolled a small proportion of asymptomatic patients (15% and 18%, respectively). As a result there is no convincing evidence that CRT is indicated in patients presenting with no or transient, mild symptoms and the recommendations in the new guidelines are restricted to patients in NYHA II class. Specifically, CRT preferentially by CRT-D is recommended to reduce morbidity or to prevent dis-
ease progression (Class I, Level of evidence A) in patients with NYHA function class II, LVEF ≤35%, QRS ≥150 ms, sinus rhythm, and optimal medical therapy.11,18-20

To conclude, improvement is primarily seen in patients with QRS ≥150 ms and typical LBBB, survival advantage is not established, and in MADIT-CRT the extent of reverse remodeling was concordant with, and predictive of, improvement in clinical outcomes.

A few months after the publication of the ESC Guidelines, a new important study was published, RAFT (Resynchronization/defibrillation for Ambulatory heart Failure Trial). RAFT enrolled 1798 NYHA class II or III HF patients with an EF <30% and an intrinsic QRS ≥120 ms or a paced QRS ≥200 ms, and randomized them 1:1 to an ICD alone or an ICD plus CRT (CRT-D).22

It should be mentioned that only 20% of patients had NYHA class III HF at study entry. After a mean follow-up of 40 months, the risk of occurrence of the primary end point (hospitalization for HF or death) was significantly reduced by 25%, from 40.3% in the ICD-only group to 33.2% in the CRT-D group (P<0.001). Moreover, mortality was also reduced by 25% (hazard ratio, 0.75; P=0.003), from 26.1% in the ICD-only patients to 20.8% in the CRT-D patients. Specifically, in NYHA class II patients, RAFT showed a significant 29% reduction in mortality (P=0.006), whereas in NYHA class III patients the reduction in mortality was nonsignificant (21%, P=0.14).

When comparing 2-year mortality rates in patient treated with CRT devices, RAFT showed about 20% 2-year mortality in the CRT-D arm, which is comparable with about 18% 2-year mortality in CARE-HF, the trial enrolling class III and IV patients, and comparable with a 25% 2-year mortality observed in the CRT-D arm of the COMPANION trial, which also enrolled class III and IV patients.

These rates are much higher than the 6% 2-year mortality observed in MADIT-CRT patients randomized to CRT-D therapy. RAFT seems to be more similar to CARE-HF or COMPANION than to MADIT-CRT, which probably explains the differences between trials regarding the magnitude of the effect of CRT-D on HF events and differences in the effect on mortality. Long-term follow-up of MADIT-CRT patients will possibly allow us to determine whether in these mild HF patients, CRT-D also reduces mortality, which would be expected after about a 40% reduction of the risk of HF events.

**New guidelines for CRT-P/CRT-D in patients with heart failure and permanent atrial fibrillation**

The majority of randomized CRT studies to date have been almost exclusively restricted to patients in sinus rhythm, although approximately 1/5 of patients receiving CRT in Europe have permanent atrial fibrillation (AF).

However, since the publication of the previous guidelines on CRT, several studies in addition to a meta-analysis have been published.23-25 The majority of patients in this meta-analysis had undergone atrioventricular (AV) nodal ablation. A large, prospective, observational registry26 showed that, during long-term follow-up, hybrid therapy combining CRT with AV ablation (resulting in 100% effective biventricular stimulation) conferred improvements in LV function and exercise capacity comparable to those achieved in patients with sinus rhythm. In the same cohort,27 the authors provided evidence that patients with HF and AF treated with CRT received the same survival benefit as that achieved in patients with sinus rhythm only when AV ablation was performed shortly after CRT implantation.

Summarizing the existing data, there is consensus that essentially complete ventricular capture is mandatory in order to maximize clinical benefit and improve the prognosis of patients with permanent AF. Thus, AV nodal ablation may be required to assure adequate pacing. The evidence is strongest for patients with an LBBB pattern, and there are not sufficient data for mortality recommendation.

The new guidelines for CRT in patients with HF and permanent atrial fibrillation (AF) recommend that CRT-P/CRT-D should be considered to reduce morbidity in patients with NYHA function class III/IV, LVEF ≤35%, QRS ≤130 ms and pacemaker dependency induced by AV nodal ablation (Class IIa, level of evidence B).

CRT-P/CRT-D should be also considered to reduce morbidity in patients with NYHA function class III/IV, LVEF ≤35%, QRS ≤130 ms and slow ventricular rate and frequent pacing defined as ≥95% pacemaker dependency (Class IIa, Level of evidence C).

**New guidelines for CRT-P/CRT-D in patients with heart failure and a conventional pacemaker indication**

Taking into consideration the fact that prospective randomized controlled studies specifically addressing the issue of CRT in patients with a narrow QRS complex are currently lacking and there are only several retrospective observational series or small prospective trials demonstrating a clinical benefit, the level of recommendations is B or C.

Specifically, in patients with HF and a concomitant class I pacemaker indication, CRT-P/CRT-D is recommended to reduce morbidity in patients with NYHA function class III/IV, LVEF ≤35% and QRS ≥120 mms (Class IIa, Level of evidence B).28-35

It is also stated that CRT-P/CRT-D should be considered to reduce morbidity in patients with NYHA function class III/IV, LVEF ≤35% and QRS <120 ms (Class IIa, Level of evidence C).
Concerning patients with NYHA function class II, CRT-P/CRT-D is recommended to reduce morbidity in patients with LVEF≤35% and ORS<120 ms (Class IIb, Level of evidence C).

New guidelines for LV assist device as destination therapy for patients with severe HF ineligible for cardiac transplantation

Patients with end-stage HF have a poor quality of life, a very high mortality rate, and are potential candidates for implantation of a LV assist device. Although cardiac transplantation is associated with high 1- and 10-year survival rates, organ supply is limited. The technical improvements and proven success of implantable LV assist devices have made it a reasonable treatment option in these patients, either as a bridge to cardiac transplantation or as destination therapy. Patient selection for an LV assist device is crucial. Patient population mainly consists of patients on inotropic (and/or mechanical) support prior to LV assist device implantation

Patients with severe renal, pulmonary, or hepatic dysfunction as well as patients with active infection or cardiogenic shock should not be considered as candidates. Data from the National Institutes of Health (NIH) supported INTERMACS registry (Interagency Registry for Mechanically Assisted Circulatory Support) indicate that approximately 10% of patients in clinical practice receive an LV assist device as destination therapy. The available evidence suggests that a continuous flow device is superior to a pulsatile flow device. However, no controlled data is available as bridge to cardiac transplantation.

The new guidelines for LV assist device in patients with severe HF ineligible for transplant state that LV assist devices may be considered as destination treatment to reduce mortality in patients with NYHA function class III/IV, LVEF≤25% and peak VO2<14 mL/kg/min. (Class IIb, Level of evidence B).

Conclusion

The new ESC Guidelines set new standards of clinical excellence and their implementation is expected to have a major impact in clinical practice in reducing the complications of HF. The ESC has as a strategic priority: not only the production of high-quality guidelines, but also their correct implementation. The national societies have shown interest and understanding with regard to the need for implementation. What is needed is systematic and organized collaboration between national societies and the ESC and an assessment of the results on an annual basis.
France’s masterpiece of intangible heritage goes global:

French master chefs abroad

I. Spaak, France

Cooking with heart, for the heart:

The French recipes of the ESC European Cook Book—Tidbits of history and etymology

R. Ferrari, Italy
A TOUCH OF FRANCE

Cooking with heart, for the heart:
The French recipes of the ESC European Cook Book
Tidbits of history and etymology

by R. Ferrari, Italy

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The European Cook Book: Healthy Diets, Healthy Hearts was published in 2010 by the European Society of Cardiology (ESC) as part of the European Heart for Children (EHC) initiative, as one of the ways to raise income for this newly founded humanitarian nonprofit organization. It called on contributions from all member cardiological societies of the ESC, the largest cardiological society in the world, with more than 85,000 members representing 53 countries in Europe and around the Mediterranean, including a number of Affiliate Societies in more distant parts of the world. The European Cook Book, edited by Roberto Ferrari and his wife, Claudia Fioria, starts by giving solid science, with an overview of the major cardiovascular diseases and thorough dietary explanations. This is followed by the recipes, with 44 countries having contributed a heart-friendly menu consisting each of a complete meal, with first course, main course, and dessert, all of which epitomize their respective countries’ culinary traditions and prove that dietary cooking by no means need be a dreary, boring, and bland chore, but that it can be both exciting and a mouth-watering offering to the taste buds. This article focuses on the recipes provided by one country, France, to explore their cultural, historical, and etymological underpinnings, with surprising findings!

Medicographia. 2011;33:458-467 (see French abstract on page 467)
European Heart for Children (EHC)* is a humanitarian non-profit organization aimed at addressing the plight of children with congenital heart disease (CHD) in the poorer member countries of the European Society of Cardiology (ESC)†, the world’s largest cardiological society, totaling more than 65,000 members from 53 National Societies in Europe and the Mediterranean and 36 Affiliated Societies throughout the world. The original idea for EHC came to my wife, Claudia Florio, an erstwhile linguist and translator who went on to become a screenplay author and film director. As I started my presidency of the ESC (2008-2010), she became interested in CHD and realized that its treatment was sub-optimal in several of the ESC National Societies’ countries. She convinced me and the incoming ESC President, Michel Komajda, to establish a foundation whose mission was “To promote knowledge and treatment of CHD and related disorders in children and young adults in the ESC member countries and beyond.” This project was presented at the entire membership of the ESC at the Annual Congress in Barcelona in September 2009, was approved by the ESC Board, and the project was launched.1

One of the ideas that was triggered by this project was to publish a book—European Cook Book: Healthy Diets, Healthy Hearts— that would deal with the prevention of cardiovascular diseases, and give advice on how to improve our lifestyle, in particular our eating habits. This book, edited by myself, Claudia Florio, and lavishly illustrated with photos by Paolo Zappaterra, was to be dedicated to the EHC, with income raised from its sale going directly to the newly established organization. The guiding idea was to avoid writing a dreary book with uninspiring dietary advice, and instead encourage a healthy diet without losing the pleasure of eating.

Each ESC National Society and Affiliate was invited to contribute a typical menu that they would recommend as healthy. All menus were scrutinized by a nutritionist to make them more healthy where needed, following the instructions laid out in the first, scientific part of the book. This formed the basis of the European Cook Book. This book is more than a mere collection of recipes, as it endeavors above all to serve an educational purpose, explaining what cardiovascular diseases are and providing suggestions on healthy ingredients and food preparation. Its table of ingredients allows the reader to prepare favorite recipes, making them healthier just by adjusting the proportion of “good” or “bad” ingredients.

One of the unexpected discoveries made while preparing this book was that it proved to be also a cultural adventure. One salient aspect is that European cuisine is a fusion of the Greek and Roman culture based on agriculture (fruit and vegetables), olive oil and wine—the forerunner of the much touted “Mediterranean diet,” and of the Nordic culture based on hunting (meat), beer, and butter. The gradient and consequently the interaction between the two cultures becomes very evident to the reader while sampling menus typically from northern Europe or those of the southern Mediterranean countries.

Writing in the “Touch of France” cultural section of Medicographia, I thought it would be interesting to take a closer look—not at French culinary culture in general—but specifically at the recipes provided by the French Cardiological Society and, beyond the purely gastronomic aspects, hunt for some of the deeper cultural, historical, and even etymological underpinnings of those recipes. What I discovered was so fascinating, that it clearly calls for further forays into the cultural aspects of all the other countries represented in the European Cook Book—but that’s another story!

I start by giving a comprehensive list of the dishes proposed by the contributors (Table I, page 460 & 461), before focusing on the three recipes provided by the French Cardiological Society: Bouillabaisse, chicken in a pot, and Bourdaloue pear tart, and invite you to enjoy a gustatory and cultural voyage!

Bouillabaisse

Bouillabaisse, France’s most celebrated soup—a stew really—(together with the no less famous “soupe à l’oignon” or onion soup) is the first course given in the European Cook Book by our colleagues of the French Cardiological Society. It is redolent of Provence, lavender, anisette, Marcel Pagnol and his theater trilogy Marius, Fanny, and César,” and above all of its birthplace, Marseille and its “Vieux Port” (Old Port).
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<td>Albania</td>
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<td>Baked fish with onions and tomatoes &amp; Leek pie</td>
<td>Cheese mousse</td>
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<td>Austria</td>
<td>Austrian pancake soup (Frittatenaupe)</td>
<td>Wiener Tafelspitz</td>
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<td>Belarus</td>
<td>Cold sorrel soup</td>
<td>Stuffed cabbage rolls</td>
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<td>Bosnia and Herzegovina</td>
<td>Pan-fried aubergines</td>
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<td>Bulgaria</td>
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<td>Baked peppers stuffed with cabbage</td>
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<td>Czech Republic</td>
<td>Vegetable soup</td>
<td>Rabbit loins with grapes and tarragon &amp; Vegetable cake</td>
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<td>Denmark</td>
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<td>Finland</td>
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<td>Arctic char with mushroom and parsnip purée</td>
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<td>France</td>
<td>Bouillabaisse</td>
<td>Chicken in a pot</td>
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<td>Georgia</td>
<td>Aubergine with walnuts &amp; Tbilisi-style tarragon soup</td>
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<td>Sweet yoghurt sundae with saffron and pomegranate</td>
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<td>Germany</td>
<td>Pea soup</td>
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<td>Greece</td>
<td>Spinach rice &amp; Red beans with tomatoes and sweet paprika</td>
<td>Sea bream with mashed celeriac &amp; Roast chicken with herbs, potatoes, and orange</td>
<td>Yoghurt with amarena syrup &amp; Halvas</td>
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<td>Hungary</td>
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<tr>
<td>Iceland</td>
<td>Potato and leek soup &amp; Fresh salad with potatoes and avocado</td>
<td>Redfish rolls with spinach and prosciutto &amp; Trout in oatmeal</td>
<td>Yoghurt ice-cream with basil sauce</td>
</tr>
<tr>
<td>Indonesia</td>
<td>Cucumber pickles &amp; Mixed vegetable pickles &amp; Pickled shallots</td>
<td>Sweetcorn rice &amp; Grilled chicken with chilli sauce &amp; Grilled fish with tomato and basil sambal</td>
<td>Avocado smoothies</td>
</tr>
<tr>
<td>Israel</td>
<td>Spring stew</td>
<td>Roast chicken with lemon</td>
<td>Lemon sorbet</td>
</tr>
<tr>
<td>Italy</td>
<td>Spaghetti with swordfish</td>
<td>Anchovy pie</td>
<td>Pear tart</td>
</tr>
<tr>
<td>Latvia</td>
<td>Courgette croquettes with chanterelle mushrooms</td>
<td>Flounder with vegetables &amp; Roast venison &amp; Wild boar croquettes</td>
<td>Strawberry and rhubarb ice cream</td>
</tr>
<tr>
<td>Lebanon</td>
<td>Taboulé</td>
<td>Fisherman’s plate</td>
<td>Amar-eddine &amp; Mint tea</td>
</tr>
<tr>
<td>Lithuania</td>
<td>Pickled beetroot with goat’s milk cheese</td>
<td>Oven-baked salmon</td>
<td>Cranberry mousse</td>
</tr>
<tr>
<td>Malaysia</td>
<td>Cheese balls &amp; Soybean and sweetcorn delight</td>
<td>Grilled fish with tangy dip &amp; Bavarian beef and cabbage</td>
<td>Deep blue sea &amp; Pear and mango lassi</td>
</tr>
<tr>
<td>Malta</td>
<td>Bresaola with dried figs &amp; Marinated sun-dried black olives &amp; Crudités with olive oil &amp; Beetroot and carrot juice &amp; Warm artichoke heart salad</td>
<td>Roast beetroot &amp; Steamed broccoli &amp; Sea bass parcels &amp; thick garlic sauce</td>
<td>Orange terrine on strawberry sauce and Pear and almond tart &amp; Walnut biscuits &amp; Lemon and mint tea</td>
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</tbody>
</table>

Table I. Recipes from the participating European Society of Cardiology (ESC) Societies, Associations, and Affiliates: a mouth-watering reminder that diets needn’t be dreary.
The history of Bouillabaisse goes a long way back, to prehistoric times in fact, since fish soups/stews are attested as early as the Neolithic era. Bouillabaisse-like fish stews are also extremely widespread geographically; they are found throughout the countries bordering the Mediterranean like Greece, Spain, Italy (Roman mythology has Venus feeding such a soup to Vulcan), and further away in Portugal, Hungary, Russia, and Brazil. Its earliest appearance in France dates back to the foundation of Marseille by an ancient Greek people, the Phocaeans, in 600 BC, who called it *kakavia* (*κακαβια*, from the cauldron in which it was cooked). The dish is still popular in Greece today. Its strange name comes from the ancient Provençal variety of Occitan, from *bolhir*, meaning “to boil” and “abaissar;” meaning to reduce (the heat), let simmer: the idea was that, as soon as the soup started boiling, one had to reduce the flame (to avoid the fish disintegrating).

**From simple fishermen’s stew to three-star-rated dish**
Originally, Bouillabaisse was poor man’s fare, or rather, poor fisherman’s fare, seawater heated in a cauldron over a wood fire, with garlic and fennel, in which hungry fishermen returning to port would throw in their catch of the day of shellfish and common rockfish that were too bony for sale, saving the more marketable fish for their customers. In the 17th century, tomatoes, brought back from America, were added, then more herbs and spices such as saffron. From then onward...
Cooking with heart, for the heart – Ferrari

Bouillabaisse grew increasingly sophisticated (and expensive to make) until it became the gourmet dish it is today. Its fans tend to wax emotional about it. One author, Alfred Capus, describes it as “fish with sun in it”; A. J. Liebling, writing for the New Yorker in 1962 reminisces: “Ever since 1918, when I ate my first bouillabaisse—an event that in my mind overshadowed the end of the First World War…”; Marcel Pagnol went irate upon hearing that a restaurant had added lobster to the ingredients, labeling this “heresy.”

◆ The Bouillabaisse Charter

Actually, the list of ingredients gives rise even today to heated debate, which often grows arcane in nature, with much bandying about of scientific binominal Latin designations. Non-French fledgling Bouillabaisse cooks can throw up their toque, apron, and ladle in despair over how to procure the requisite fish needed to produce the “real” thing. Fish names are notoriously complex in any given language, one fish often being called by numerous names, local names, or nicknames, and attempts at translation are often a nightmare. Also, since the 19th century, Bouillabaisse grew so popular that inspired chefs started improvising and adding ingredients at their whim and fancy. This brought about cries for a crackdown. Just as Cardinal Richelieu, in 1635, created the Académie Française to preserve and regulate the French language, a group of local restaurateurs from Marseille decided, in 1980, to draft a very official “Bouillabaisse Charter” to preserve the quality and noblesse of this dish. Charter signatories have by now been joined by members in other French cities, and abroad in other countries such as Switzerland and Morocco. The Charter states that any genuine Bouillabaisse should include at least four of the listed types of fish/shellfish/crustaceans (I’m following the official translation provided by the Charter members, let no one blame me for any ichthyological faux-pas! — I would also add that several “official lists” coexist, which doesn’t always make things simple! Final point, in brackets and italic, I give the French names). I quote (Table II):
The recipe

Peter Mayle, author of One Year in Provence, a book that propelled him instantly into worldwide fame, writes of Bouillabaisse in Provence A-Z, his ultimate guide to the goodies, sights, and mores of Provence: “It has been invariably described as a stew, a soup of gold, a mystical synthesis, beach food, a divine seduction, or the reason God invented fish.” I would add that it is also probably the reason God invented restaurants, as, to be quite frank, producing a real Bouillabaisse in one’s own kitchen is a daunting experience, both in getting the proper fish and because of the complexity of the recipe and the time involved! Far easier for us harried cardiologists is to repair to a “Bouillabaisse Charter–certified” gastronomic temple such as, for example, “Restaurant Miramar” in Marseille, get the “real McCoy” and— as our Germans cardiologist colleagues like to say— “be happy as God in France!” However, for those not faint of heart who would like to take up the challenge of preparing their own Bouillabaisse according to the French Society of Cardiology recipe, I refer you to the relevant section in the European Cook Book as it would take up too much space to be reproduced here, and much would be redundant with the description I gave of the Bouillabaisse Charter ingredients!

Chicken in a pot, aka “poule au pot”

Good King Henry

Henry IV (1553-1610) is probably one of France’s most iconic kings, and arguably one of the best rulers the country ever had. He is credited with bringing peace and prosperity to France after more than forty years of religious wars between the Catholics and Protestants (Huguenots) and signing the Edict of Nantes (1598) which guaranteed the rights of the Huguenot minority. He restored a strong monarchy and—a genuine role model for today’s troubled economy— ruthlessly overhauled French finances, drastically reducing the national debt. He saved forests from devastation, built much-needed highways and waterways, promoted agriculture, education, and the arts, financed Samuel de Champlain’s expedition to North America, thereby laying France’s claim to Canada. A conciliatory and conciliatory king, he was much loved by the populace, and has gone down in history as “Good King Henry.”

The King of the white plume and boiled chicken

King Henry IV is famously remembered for his tragic end. He was stabbed to death by Ravaillac, a fanatical catholic, on 14 May 1610. The blow pierced his left lung and severed the vena cava and the aorta, bleeding the king to death within minutes. Such a quick demise was not to be the fate of his murderer—an event that is deeply etched in the collective soul of France. The assassination of Henry IV by Ravaillac on 14 May 1610. Painting by Charles-Gustave Houssez (1822-1894). Oil on canvas, 1860, 140×118 cm, Musée du Château de Pau, Dépôt du Musée d’Orsay, © RMN/René-Gabriel Ojéda.
memory of the French. Ravaillac was made to suffer a long, painful death over an entire day, tortured with pincers, molten lead and boiling oil and pitch poured into his wounds, his right hand coated with sulfur and set ablaze (an extra specifically reserved for regicides), before being dismembered by four horses, his body burnt and ashes scattered. Voilà!

But Henry IV also remains well-remembered to this very day thanks to four famous historical quotes that are part of every French person's historical heritage. The first is a rallying cry that the future king uttered while taking lead in a battle, exposing himself to great personal risk: “Follow my white plume….”

The second was his comment after having converted from Protestantism to Catholicism, which was the precondition for being accepted by the Parisians and acceding to the throne: “Paris is well worth a mass.” The third quote is actually from his visionary minister, Sully, but epitomizes the King's economic priorities: “Plowing and grazing are the two teats of France.” (a quote guaranteed to elicit giggles in the class-room at the tender age at which this period of French history is usually taught). The fourth quote is a solemn vow for which Henry IV is most fondly remembered for and which directly concerns the main course cited by the French Society of Cardiology in the European Cook Book: “If God keeps me, I will make sure that there is no working man in my kingdom who does not have the means to put a chicken in the pot every Sunday.” His fame would have probably skyrocketed all the way up to lay sainthood in the eyes of present-day French school kids if he in fact had rather been the inventor of the all-time favorite “poulet-frites,” ie, roast chicken with (for readers across the Atlantic) French fries or (for those across the Channel) chips. Of course, it wouldn’t have been such a heart-friendly recipe in that case!

Table III. Recipe of Chicken in a Pot

<table>
<thead>
<tr>
<th>Poule au Pot – Chicken in a Pot</th>
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</thead>
<tbody>
<tr>
<td>Serves 4</td>
</tr>
<tr>
<td>1 medium-sized chicken</td>
</tr>
<tr>
<td>2 onions</td>
</tr>
<tr>
<td>4 leeks</td>
</tr>
<tr>
<td>3 carrots</td>
</tr>
<tr>
<td>4 small turnips</td>
</tr>
<tr>
<td>1 stick of celery</td>
</tr>
<tr>
<td>3 bay leaves</td>
</tr>
<tr>
<td>small bunch of parsley</td>
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<tr>
<td>400 g of button mushrooms</td>
</tr>
<tr>
<td>1tsp of coarse low-sodium salt</td>
</tr>
<tr>
<td>freshly ground pepper</td>
</tr>
<tr>
<td>2 cups of rice</td>
</tr>
<tr>
<td>1 tbsp of extra virgin olive oil</td>
</tr>
</tbody>
</table>

1. Wash the chicken under cold water.
2. Put the chicken in a cooking pot that is slightly larger than the size of the chicken.
3. Cover the chicken with water and add the salt, pepper, and bay leaves. Place a lid on the pot, bring to the boil and simmer.
4. Peel and chop the vegetables.
5. Add the carrots and turnips to the pot.
6. Leave the chicken stock to cook for 30 minutes. Then add the leeks, chopped onions, and parsley and cook for another 30 minutes.
7. Drain off about 4 cups of the stock into a separate pan. Replace the lid and cook for a further 15 minutes.
8. Filter the drained stock well, or allow it to cool and then dispose of any fat that comes to the surface.
9. Add 2 cups of rice to the filtered stock and cook until the rice is done.
10. Trim the ends of the mushrooms, clean and cut them into quarters, then briefly sauté them in a pan with 1 tbsp of olive oil.
11. Serve the mushrooms piping hot with the chicken and rice.

Courtesy of European Society of Cardiology. The European Cook Book: Healthy Diets, Healthy Hearts. Recipes from the French Society of Cardiology, pp 151-152. © 2010, European Society of Cardiology.
The recipe
At his birth in 1553 in Pau, in the Province of Béarn in the Southwest region of France, the future king’s lips were rubbed with garlic and he was made to smell a cup of wine. This was a common practice with the newborn, to prevent disease. With hindsight: Southwest of France, garlic, and wine: wasn’t this the very first hint of the “French Paradox?” The recipe of “poule au pot,” a restorative chicken stew with vegetables, has been made even healthier in the European Cook Book with its suggestion to drop the originally included rich white sauce, use low-sodium salt, olive oil, and skin the chicken before cooking. This is how it goes (Table III).

Bourdaloue pear tart: surprising eponyms

Preaching in the “dessert?”
Louis Bourdaloue (1632-1704), from whom this dessert takes its name, was a 17th-century Jesuit and renowned preacher. His eloquence was compared to none other than that of Corneille and Racine. The philosopher Voltaire—no friend of the Church—praised him as surpassing even Bossuet at the pulpit, as much for his language as for his compelling reasoning and convincing proofs. He would preach with closed eyes and was nicknamed the “King of Preachers and Preacher to the Kings.” His style of speech has been praised as the most perfect in French history, and yet he was understood by all. Like Bossuet, many of his sermons were taken up in schoolbooks and became an integral part of French classical literature. Bourdaloue was repeatedly invited to deliver spiritual Advent and Lenten sermons at the court of King Louis XIV, a noteworthy total of eight times, which was all the more remarkable as preachers were called a maximum of three times to court. Even Protestants fell to his fiery eloquence and converted in droves. His secret was his knack of adapting to the most diverse of audiences, whether king or beggar. At the end of his life he devoted his ministry to the poor, prisoners, sick, and ailing in hospitals, prisons, and charitable institutions, still drawing crowds.

Unexpected etymological developments
Bourdaloue was undoubtedly a spellbinding preacher, but also somewhat of a marathon talker, addicted to prolixity. So much so that his interminable sermons (often lasting over three hours) could be quite trying on parish bladders, particularly those of the gentler sex. As the story goes, some “canny” craftsman came up with just the right answer to keep the call of nature from jeopardizing the benefit of unabridged spiritual edification. Thus the more provident ladies—not unlike the Gospel’s wiser virgins with their lamps—would equip themselves with oblong portable (note the adjective, its relevance will be made clear very shortly) chamber pots, which they would conceal under their dresses (no miniskirts in those days!), and thus avoid having to leave their stalls or pews and lose the precious theological thread. Quite naturally, these chamber pots became eponymously known as “Bourdaloues.” From there it was a short step from undergoing corruption—perhaps by some English visitors lured to Paris by the preacher’s fame—to “portaloo” then “portable loo” and, as the British are known to like short crisp words, simply “loo”: QED, quod erat demonstrandum! Be that as it may, there are two other anecdotes that have been invoked to explain to the etymology of “loo,” for some unfathomable reason always linked to France.

One derives the word “loo” from Waterloo, with the first recorded use coming from James Joyce’s Ulysses (1922): “O yes, mon loup. How much cost? Waterloo. Water-closet.” Another theory derives the word “loo” from a French word of caution going back to the days when chamber pots were nonchalantly emptied out of windows directly onto the street: “gare à l’eau,” which translates as “watch out for the water” (water is a well-known euphemism for urine, as in “pass water”). Some poor sul lied English tourist (perhaps a revenge for Waterloo…) misunderstood the phrase as “gardyloo,” which, again, was then shortened to “loo.”

◆ The recipe

◆ Unexpected etymological developments

To access the complete article, please refer to the original source.
Bourdaloue also left his name to a type of thick, corded ribbon used to stiffen seams, button bands and belts, and with which the preacher was wont to adorn his hats. In English, there is a similar eponymous derivation from Viscount Petersham (1780-1851), an army officer, with “petersham” also designating a ribbon as well as an overcoat made of heavy woolen fabric.

Tarte Bourdaloue — Bourdaloue Pear Tart

Serves 6

- 4-5 pears
- sliced blanched almonds for decoration (optional)

Pastry:
- 250 g of flour
- 100 g of sugar
- 50 g of butter
- 1 egg

Almond cream:
- 50 g of soft butter
- 50 g of ground almonds
- 1 egg

Pastry:
1. Mix the sugar and the flour, add the butter and knead until crumbs are formed.
2. Add the egg (and a small amount of water if necessary) and work the dough in the palm of your hand until it forms a shortcrust pastry and is dry to the touch.
3. Leave to rest in the fridge for at least one hour.
4. Roll out the pastry and use it to line a pastry case.

Almond cream:
1. Whisk the butter and the sugar until light and fluffy.
2. Add the egg and mix well.
3. Add the ground almonds.
4. Blind bake the pastry case.
5. Once ready, add the almond cream to the case. Place the sliced pears (or halved pears) into the cream. Sprinkle the almonds on top of the pears.
6. Bake the tart in the oven at 180° for 30-40 minutes.
7. Serve either warm or cold.

Courtesy of European Society of Cardiology. The European Cook Book: Healthy Diets, Healthy Hearts. Recipes from the French Society of Cardiology, pp 151-152. © 2010, European Society of Cardiology.

Table IV. Recipe of Bourdaloue Pear Tart.

“Bourdalouses” were urinals shaped to the female anatomy and used to relieve the pressure on pious ladies’ bladders during Louis Bourdaloue’s long sermons. They were also called “coach pots” as they helped ladies endure long coach journeys. Their heyday was during the reigns of kings Louis XIV and Louis Philippe. In those days ladies wore long crinoline dresses and lower undergarments with unjoined legs, explaining their ease of use, hence yet a third name: “crinoline slippers.” Some of these urinals had pattern-matching china lids. Now coveted collectors’ items, they usually fetch between €200 and €1000 at auctions. In 2006, a rare snail-shaped bourdaloue dated 1752 changed hands for a hefty €25 000.

The recipe

But back to our topic of "Tarte Bourdaloue." It will perhaps come to some readers as a double anticlimax to learn that although the name of this tasty pear-and-almond pie does hark back to Bourdaloue, it is in a somewhat removed way, since it has nothing to do with a particular delicacy characterizing the preacher’s possible proneness to the Sin of Gluttony, but simply to the fact that the confectioner—Monsieur Fasquelle—who invented this recipe in 1824, one hundred years after the preacher’s death, happened to have his bakery on the rue Bourdaloue in Paris.

The other cause for a feeling of anticlimax, is that the French Society of Cardiology included the recipe of “Tarte Bourdaloue” in the European Cook Book, albeit while issuing a strong caveat, since, to quote them: “This recipe is very rich in saturated fats and is not suitable for people with heart problems or those following a strict low-fat diet.” They do, however, strike a note of optimism by adding, “However, we are including it here, as it is unlikely to do much harm if consumed once a year, on a special occasion such as Christmas, for example.” Thus the safe enjoyment of “Tarte Bourdaloue” depends on a proper sense of measure,—as do so many things—and Bourdaloue would certainly agree to that. He was much appreciated by his flock who well knew that “although austere in his behavior and character, he was, as a priest, as indulgent as his duties allowed him to be.”

So, with Father Bourdaloue’s forgiveness and blessing, this is how to prepare your dessert (Table IV). ■

References
When Paul Bocuse discovered that his Japanese students had memorized his recipes “to within a gram”, he declared “Gentlemen, we’ll improvise.” “That I think was what most shocked them. But they learned that French cuisine is an improvisation and not a science to be followed to the letter. Cooking is like a painting: it is created in the here and now, by an artist drawing on his experience and taste.”

France’s masterpiece of intangible heritage goes global: French master chefs abroad

by I. Spaak, France

As railway lines spread across Europe during the second half of the 19th century and the vacationing aristocracy flocked to the great hotels, Frenchman Auguste Escoffier was plotting a culinary upheaval. This “king of chefs and chef to kings” codified haute cuisine, adapted recipes to international standards, invented new ones, and revolutionized gastronomy by organizing his kitchens in “brigades,” each person being allotted a specific task in the preparation of a dish. Where once, for example, a single cook took 15 or more minutes to prepare eggs Meyerbeer, an Escoffier brigade slashed the time needed, as the entrée preparer cooked the eggs, the roast chef grilled the kidney, and the sauce cook prepared the truffle sauce. Escoffier brought French gastronomy to the world stage and today’s luminaries like Pierre Gagnaire, Alain Ducasse, and Guy Savoy are following in his footsteps by investing overseas and putting an international face on French cuisine. The attractions of spreading the culinary word is such that French chef and restaurateur Daniel Boulud has yet to open a restaurant in France, but is doing very nicely thank you in Palm Beach, Beijing, Vancouver, and London, not to mention Manhattan where his eponymous restaurant Daniel was in 2010 elevated to the culinary pantheon by a three-star rating (the highest possible) in the Michelin Guide. With the excellence of its products, its culinary skills and know-how, its art of preparing and presenting food, gastronomy is part of France’s cultural influence. The culinary genius of France received its official imprimatur in November 2010 when UNESCO added the gastronomic meal of the French to its list of Masterpieces of the Intangible Heritage of Humanity.

Medicographia. 2011;33:468-475 (see French abstract on page 475)
omy by elaborating a wholly new discourse on the pleasures of the table. By the 1880s and 1890s, with the emergence of the great hotels in Europe and America, many French cooks, including Auguste Escoffier (1846-1935), France’s preeminent chef who was deploying his talents in London, at the Savoy and then the Carlton, codified an international haute cuisine and assimilated products and methods from the cooking traditions of other countries. Writings proliferated asserting the indubitable superiority of France’s gastronomy, which became a byword for the French and their way of life.

Recent decades have seen a renewal of country cooking and increasing diversification of sources and outlooks, but France’s role as undisputed leader is no longer assured. Alain Ducasse, Joël Robuchon, and other French culinary stars have even been reproached for deserting their kitchens to don the suits of company chairmen, of being haughty, amateurish, of doing little but jet around the world from one of their restaurants to another. Some faultfinders have even dared take a swipe at national treasure Paul Bocuse, or Monsieur Paul as he has long been known, just as yesteryear others showered praise upon Escoffier only later to pan him.

And to cap it all, Restaurant magazine’s 2011 World’s 50 Best Restaurant Awards, based on a poll of international chefs, restaurateurs, gourmards, and critics, include but one French eatery in the top ten (at number 9, Le Chateaubriand in Paris). Out ahead are Denmark at number one, three Spanish restaurants, Italy, the UK, the USA, and Brazil. But France does have 8 in the top 50, more than any other country (Italy and US come in second with 6 each; Spain has 5, the UK 4). It’s true that French chefs run three of the five three-star restaurants in the Michelin New York 2011, and number 11 on the list is the Manhattan restaurant Daniel which, although listed under the US, is actually the flagship restaurant of Frenchman Daniel Boulud. Joël Robuchon is at number 14, Pierre Gagnaire 16, Michel Troisgros 44, and Alain Ducasse at 45 is down four from 2010.
France’s self-esteem may have taken a knock, but all is not lost. On 16 November 2010, UNESCO added the gastronomic meal of the French to its list of Masterpieces of the Intangible Heritage of Humanity. “For France cuisine is not simply the product of a long historical tradition, but also one of the most accomplished expressions of the excellence of its products, of the quality of its culinary know-how, of its cultural influence,” noted the French Prime Minister. A heritage, then, that has its followers and whose chefs are still able to rustle up a decent meal while running a restaurant which, in Pierre Gagnaire’s view, “faces tomorrow but is respectful of yesterday.”

In the words of UNESCO: “The gastronomic meal emphasizes togetherness, the pleasure of taste, and the balance between human beings and the products of nature. Important elements include the careful selection of dishes from a constantly growing repertoire of recipes; the purchase of good, preferably local products whose flavors go well together; the pairing of food with wine; the setting of a beautiful table; and specific actions during consumption, such as smelling and tasting items at the table. […] The gastronomic meal draws circles of family and friends closer together and, more generally, strengthens social ties.”

### Foie gras hamburger in New York

To celebrate the 60th birthday of his best friend, Daniel Boulud spent 24 hours flying to New Zealand, where he stayed for just 36 hours. Grilled langoustines, roast leg of lamb, great wines, an exquisite repast well worth the trip. But how can one imagine that the simplicity of these New Zealand spreads, hearty and delicious though they were, could be a red-letter day among the gastronomic memories of the French culinary maestro? Was this mere whimsy, a desire to return to simpler fare of someone who has been delighting the taste buds of New Yorkers for two decades with dishes of extreme sophistication? Had Boulud decided to renounce teamwork, those myriad acts of numerous creators of a single dish advocated by Auguste Escoffier, high priest of French cuisine at the end of the 19th century? Not a bit of it. For if New York’s swells hasten to Boulud’s three-star Manhattan establishment Daniel, it is precisely because its creator has succeeded in producing a blend of French manners and decorum, country cooking, and appreciation of fine produce that tickles the palates of the most discerning of his adopted countrymen and women. The proof is in the pudding: vanilla slow-cooked rhubarb with yogurt mousse, caramelized phyllo, and acacia honey ice cream. Not to mention the main course: grilled Alaskan king salmon with chanterelle, wilted spinach, spring garlic, and green peppercorn sauce.

A farmer’s son, Boulud was born in 1955 in Saint-Pierre-de-Chandieu in east-central France near Lyon, which is often seen as the French capital of gastronomy. He left home at 14 to take an apprenticeship in catering, spent time working in Georges Blanc’s three-star restaurant at Vonnas, studied in Mougins with Michel Vergé who inculcated in him the spirit of adventure, worked briefly for Michel Guérard, left for Denmark, and then flew to Washington to run the kitchens of the European Commission’s representative in the United States. After which there was no stopping him. New York City, that lodestone for so many, beckoned. He opened the Polo Lounge at The Westbury Hotel, then Le Régence at the Hotel Plaza Athénée, before in 1986 taking up the position of Executive Chef at Le Cirque, a favorite with Jackie Kennedy and the Duchess of York. In 1993, he opened on Manhattan’s Upper Eastside his own restaurant Daniel, which was soon lauded by the critics. He relocated Daniel in 1997 to premises at Park Avenue and 65th Street recently vacated by Le Cirque, and relaunched the original Daniel as the Café Boulud, aimed at a more informal clientele. In 2001 at Manhattan’s “midtown crossroads of fashion and theater,” Boulud opened the db Bistro Moderne for casual dining. Some might balk at 32 dollars a throw for a burger, but then it’s sirloin and braised short ribs plus black truffles and foie gras on a Parmesan bun. And anyway Boulud makes light of such
demurral by reminding skeptics that his skills are rooted in
the culinary arts of the French tradition. Meanwhile, he is
opening restaurants around the world, always observing
the same principle: dare to use regional traditions to enrich
French-style gastronomy, the internationalized version, with
a menu adapted to local tastes, served in a setting with an
elegant interior design. At the five-star JW Marriott Marquis
in Downtown Miami, for example, with its whitewashed oak
floors and paneling, steel gray canvas and leather upholstery,
geometric patterned ceiling, and street-level terrace over-
looking the Miami River, there is duo of beef, mustard crust-
ed ribeye, braised short rib, sweet garlic pommes puree, as-
paragus, and fava beans. In Palm Beach, try herb-scented
halibut, foraged spring vegetables, fiddlehead ferns, miners
lettuce, morels, ramps, arbequina olive oil emulsion. And the
Bar Boulud at the Mandarin Oriental Hyde Park in Kensing-
ton, London, offers black sea bream, sautéed baby gem let-
tuce, brown shrimp, lemon confit, and sourdough croutons. In
Beijing, at the manor house once home to the United States
Embassy, near Tiananmen Square, now the Maison Boulud,
the décor is of pale sculpted pine wood trim, richly textured
velvet upholstery, parquet floors in dark walnut, others in
checkerboard black and white, all very 18th century, and the
focal point a mural inspired by the fountains of Versailles. On
the menu: lobster, kataifi crusted with brussel sprouts marmalade, honshimeji
mushrooms, chestnuts, walnuts, and sherry wine. And Boulud opened his
most recent establishment, the db Bistro
t Moderne, in Singapore in the fall of
2010 in the luxury dining and retail atri-
um of the Marina Bay Sands Resort.

As the praise rang out and Daniel in
Manhattan received a third Michelin
Guide star in 2010, Daniel Boulud hit
on the concept of a Bar and Lounge, a
more laid-back establishment adjoin-
ing Daniel. Not cheaper, but more flex-
ible, with no slackening of the rituals of
service. Between Madison Avenue and
Park Avenue, the casually elegant Bar
and Lounge attracts a literary lunchtime
crowd from local publishing houses, as
well as local residents—Woody Allen
and Michael Douglas among others—for dinner, late-night desserts, or cocktails like a white cosmopolitan (vodka, St. Germain elderflower liquor, lime juice, white cranberry juice), a summer in Paris (raspberries, vodka, lychees), and strawberry and pearls (strawberry margarita, Cointreau, strawberry pearls).

Cuisine as a painting

When Paul Bocuse discovered that his Japanese students had memorized his recipes “to within a gram”, he declared “Gentlemen, we’ll improvise.” “That I think was what most shocked them. But they learned that French cuisine is an improvisation and not a science to be followed to the letter. Cooking is like a painting: it is created in the here and now, by an artist drawing on his experience and taste.”

At this time Bocuse was the face of haute cuisine outside France and, together with his peers—Raymond Oliver, Michel Guérard, Alain Senderens, Roger Vergé—he was blowing a breath of fresh air into the traditional French kitchen, with its (over)elaborate and rich recipes handed down year after year. With menus adapted to the culinary habits of the four corners of the planet, Daniel Boulud has learned this lesson. Improvisation and a light touch are his watchwords. Plus discipline and order. At Boulud’s Daniel, in the kitchen and restaurant, the culinary score is interpreted with the same rigor, each playing his or her part as advocated by Auguste Escoffier.

One of Escoffier’s legendary “kitchen brigades” at the Hôtel Majestic in Nice, in 1910. Collection Dupondt/akg-images.
“King of chefs and chef to kings,” Escoffier introduced French haute cuisine to the world at the time of the boom in the great hotels that accompanied the new vogue in rail travel. The aristocracy came out from behind the closed doors of their stately homes to dine in high-class establishments, women with men. The personalized service demanded organization, planning, managing, streamlining. To optimize the kitchens, Escoffier set up a system of “brigades” to rationalize the multifarious tasks, with several people preparing different parts of the meal. Escoffier insisted upon spotlessness and hygiene in the kitchens and among the staff, along with silence and speed.

In his 1903 Le Guide Culinaire Escoffier favored light stocks over the rich sauces of tradition, to create garnishes and sauces that complement rather than drown the subtle flavors of dishes. He revamped country recipes according to the canons of haute cuisine, replacing basic fare by costly ingredients. And he devised unusual combinations named for well-known figures who dined at his table.

One such was Peach Melba (peaches and raspberry sauce accompanying vanilla ice cream) at the Savoy in London in the 1890s, in honor of the Australian operatic soprano Nellie Melba (1861-1931), whose triumph in Wagner’s Lohengrin was celebrated at a dinner party given by the Duke of Orléans, her then lover.

Another invention attached to the name Escoffier is crêpes Suzette—caramelized sugar and butter, lemon, and flambéed with Grand Marnier—in honor of French actress Suzanne Reichenberg (1853-1924), who worked under the sobriquet Suzette and who in 1897 when playing a maid at the Comédie Française served crêpes on stage. There is though a different story of its genesis. Two in fact. The first is that in London at the Savoy, Escoffier served the Prince of Wales with crêpes according to a new recipe which he proposed to dedicate to him. The future Edward VII objected that he was unworthy and suggested instead that the crêpes be named in honor of “this young person who is with me.”

The second story moves the Prince of Wales and Suzette to Monte Carlo in the year 1895, where Henri Charpentier claimed in his autobiography to have made a serendipitous discovery: “It was quite by accident as I worked in front of a chafing dish that the cordials caught fire. I thought it was ruined. The Prince and his friends were waiting. How could I begin all over? I tasted it. I thought, the most delicious medley of sweet flavors I had ever tasted… He asked me the name of that which he had eaten with so much relish. I told him it was to be called Crépes Princesse […] ‘Will you,’ said His Majesty, ‘change Crépes Princesse to Crêpes Suzette?’ Thus was born and baptized this confection, one taste of which, I really believe, would reform a cannibal into a civilized gentleman.”

Escoffier, with his rigor and dogma, shifted French gastronomy towards science. “Cuisine, without ceasing to be an art, will become scientific and should submit its formulas, often still too empirical, to a method and a precision that will leave nothing to chance.” Through his practice and publications, Escoffier would go on to impose knowledge of French cuisine internationally. He was a visionary who even then rightly predicted that future gourmets would oversee a simplification of menus.
Culinary upheavals and the advent of molecular gastronomy

In the 1960s, up-and-coming chefs rebelled against Escoffier’s orthodoxy. Paul Bocuse, Jean and Pierre Troisgros, Michel Guérard, Roger Vergé, Raymond Oliver spurned excessive complications and instead sought shorter cooking times, used fresh products and garden herbs, seasoned with lemon juice and vinegar, served smaller portions, ditched marinades, drew ideas from the heart of the four great regions of France, favored inventiveness, and employed new cooking techniques, notably microwaving.

But come boom come bust. People complained about meager portions. Paul Bocuse was accused of jet-setting around instead of slaving over a hot stove. Above all the French were reproached for having failed to foresee the coming globalization, the interest in Asian style cooking, the Spanish troublemakers and their molecular gastronomy, the Nordic restaurateurs seeking inspiration in local dishes and reinterpreting them with brio.

Some critics railed against what they saw as a failure to move with the times, foot-dragging, nay-saying of the worst sort. It was, in a word, a French rout. Others though were delighted that France’s celebrity chefs had not cravenly jumped on the bandwagon of what they saw as culinary whim-wham. In *Le Figaro Magazine* in the autumn of 2009, the food critic François Simon admitted he hadn’t crossed the threshold of Pierre Gagnaire’s Paris restaurant in the rue Balzac for three years, for fear of finding the master in thrall to what he dubbed “molecular defractionation.” It was with infectious happiness that he wrote of his delight on tasting a “casserole of slow-cooked chanterelles and cepes embellished with thin-sliced ham (plus crustless white bread and barberries drizzled with cooking juice emulsified with amontillado).” And in keeping with this style were the ramekins of foie gras soup with Malabar pepper, green lentil gnocchi, pink onions, a hint of 50-year-old Balsamic vinegar. After which, what better than milk blended with strawberry tree honey plus fresh hazelnuts, wild purslane, a veil of flowers, and a bull’s horn (small capsicum)?

Love me!

In the pantheon of boldness, Pierre Gagnaire stands supreme. Yet he admits that “For a long time I didn’t like this job of cook. I was born into a background of traditional restaurant owners. It was noisy, rough and ready, the food very ordinary. As the oldest of five children, in my region and for my generation, taking over the farm meant taking over the restaurant. I’ve tried since to put my heart and soul into it. Finally I understood that food was a means to move people, to love them, to say to them ‘love me!’ Only very recently have I learned to enjoy eating.”

In his 2010 novel *The Prague Cemetery*, Umberto Eco invests his main character with a base gluttony on a par with his criminal tendencies. And Eco seizes the opportunity to list Parisian restaurants famous in the mid-19th century: Le Grand Véfour, Lapérouse, La Tour d’Argent, Lucas Carton. “France,” says Eco, “is the country that best constructs the myth of cooking, with all its theoreticians since Brillat-Savarin. It’s a rich, refined cuisine.” In contrast, Italy practices an “excellent poor man’s cooking and one eats well even at the last greasy spoon in Romagna.”

Pierre Gagnaire agrees. “Our cuisine is more polished, more spectacular, chauvinist cooking where the chef grandstands!” And he admits that each dish is for him a risk-taking venture, that each new restaurant he opens is a huge challenge—*Sketch* and its acid shades in London, *Pierre* in Hong Kong inspired by a Soulages painting, *Twist* on the
23rd floor of the Mandarin Oriental Hotel in Las Vegas, Reflets in Dubai, and the latest, Pierre Gagnaire in Seoul, its decor fired by the groves of the Château de Versailles.

When three-star chef Guy Savoy was quizzed by a journalist on why he’d opened a restaurant in Las Vegas and how he kept up standards in six restaurants two of which are far from Paris, the owner of the eponymous restaurant in the rue Troyon in Paris had a ready answer: “A restaurant, you’re either there all the time or never. Turning up occasionally is pointless and shows you don’t trust your staff. If you want people to take responsibility, there comes a time when they must feel independent. Those that I send overseas have the requisite professional and above all human qualities. In Vegas or Singapore, they can perfectly well cope when ‘left to themselves.’ And above all members of the overseas teams come here for training. When we open we strengthen our presence on the spot with people from here.” Following Japan’s example, the United States, China, and the Gulf States are now welcoming with open arms French restaurants whose owners vie with each other to woo new customers. These investments are costly, but not always profitable. Take Alain Ducasse: his baptism of fire was almost a complete flop. When he arrived in New York in 2000, the press branded him a “sermonizer” and laid into him for having only one sitting, as in great restaurants in France, rather than the two or three sittings of New York’s finest dining places. Ducasse finally won them over and makes sure that diners know which menu items are “as American as apple pie”: Colorado lamb, Maine lobster, Yukon gold potatoes, farm-raised Berkshire pork, Pennsylvania squab, California sea urchin, Alaskan king crab, shredded Nebraskan beef. In the long term, these “bridgehead” restaurants drum up custom for the original one. As Guy Savoy notes, “the restaurants in Singapore and Vegas bring in customers here. Over the last two years we’ve had people from all over, from Uzbekistan to Djakarta! Cuisine has been evolving constantly, but today it is spreading ever further. Yet I cook the same way now as I did 40 years ago when I was doing trout and omelet at my mother’s. And it was just as good then as it is today!”

UN PATRIMOINE IMMATÉRIEL DE L’HUMANITÉ « MONDIALISÉ » : LES GRANDS CHEFS DE LA GASTRONOMIE FRANÇAISE À L’ÉTRANGER

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