

# Reduced ejection fraction heart failure – new data from multicenter studies and national registries regarding general and elderly populations: hopes and disappointments

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**Abstract:** The evaluation of patients diagnosed with impaired systolic function heart failure represents a great challenge, in both the general and elderly population. We consider that elderly patients are the most severely affected by this disease that represents the final impact of cardiovascular disease continuum. Cardiovascular diseases are associated with serious morbidity and mortality, and considerable health care costs related to diagnosis and treatment. In this report we discuss some controversies regarding methods of heart failure evaluation as well as therapeutic steps and devices, including: reparatory therapeutic steps and initiation of therapy with loop diuretics, inconsistent dose titration for angiotensin-converting enzyme inhibitors/angiotensin receptor blocker and beta blockers, as well as novel therapies, such as angiotensin receptor neprilysin inhibitor and treatments that directly improve cardiomyocyte function. We conclude that, beyond technical progress, which is raising the cost of therapy for patients with heart failure, more careful monitoring of patient progress through clinical and paraclinical control visits, both at medical facilities and at home, would have greater impact and be more cost-effective. Physical therapy and promoting emotional and psychological wellbeing, to maintain a positive state of mind, contribute substantially to the quality of life and life expectancy, and are most important in elderly people who are most affected by dramatic reductions in wellbeing. Unfortunately, for many patients with severe impairment of left ventricular ejection fraction, these goals and therapeutic procedures are often lacking in current health care systems.

**Keywords:** impaired left ventricular ejection fraction, heart failure, therapeutic controversies, elderly population

## Introduction

According to national and international public health registries, cardiovascular diseases continue to be among the leading causes of serious morbidity and mortality, and consequently contribute substantially to health care costs related to their diagnosis and treatment. Reduced cardiac output and left ventricular contractility, along with many associated comorbidities including respiratory problems, infections, and metabolic function, impair the life expectancy and quality of the lives of many individuals. The evaluation and treatment of patients diagnosed with impaired systolic function heart failure represents a great challenge, in both the general population and among elderly individuals who are the most vulnerable to this difficult-to-treat condition, partly because of the large number of associated comorbidities that such patients present with. According to registries, despite significant progress related to the diagnosis and

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treatment of heart failure, the mortality associated with this specific category of patients remains among the highest, with approximately 15%–20% of patients dying during the first year after diagnosis and around 40%–50% within 5 years.<sup>1</sup> These data have remained consistent over time, hence, heart failure represents a significant problem, even for the best performing health care systems. Moreover, the prevalence of heart failure among people older than 70 years is an important factor, as this category of patients accounts for approximately 10% of heart failure cases.<sup>2</sup> Recent studies evaluating new methods regarding medical and device therapies have introduced various diagnostic and treatment options; however, these have failed to make a major impact on mortality rates.

### Controversies regarding methods of heart failure evaluation

Significant controversies remain concerning the benefit of some therapeutic measures that have been considered standard practice for many years, as well as those introduced more recently. For example, definitions of current disease status or progression remain elusive. Currently, a number of clinical evaluation methods of depressed left ventricular contractile function are available, starting with clinical signs that unfortunately often appear at a late stage. These are used alongside laboratory tests, including natriuretic peptide level, renal function (a very specific indicator), blood count, ferritin and transferrin saturation, blood electrolytes (which are very variable, and related not only to the renal excretion performance, but also to the frequency and expertise of monitoring of cardio-active medication effects such as diuretics, including those that are potassium-sparing, angiotensin-converting enzyme inhibitors [ACEI]/angiotensin receptor blocker [ARB] or digoxin), thyroid function tests, and procalcitonine (useful for distinguishing between opportunistic respiratory tract infections and pulmonary edema).<sup>2</sup> More subtle indicators include hyponatremia (which may be more useful for predicting prognosis than hypotatremia, especially in chronic patients) and hypoalbuminemia (which, left unsupervised, may lead to unexpected therapeutic failure).<sup>3,4</sup> The reduced volume filling in patients with impaired systolic output has greater effects on the duration and the quality of life than reduced pulmonary and systemic volume loading. The tendency to hospitalize patients for depletion, without sufficient attention to the previously highlighted parameters, may lead to increased mortality rates during the first month after discharge, compared with the mortality recorded during hospitalization, leading to disillusionment concerning the prospects for long-term therapeutic control.

Of course, telemetry, or more accurately, routine use of the American system of “field” nurses specializing in brief, but daily evaluation of heart failure patients, has achieved superior results.<sup>5</sup> Close monitoring of weight, diuresis, dyspnea, body temperature, blood pressure, and cardiac frequency – basic evaluation parameters that are transmitted to a physician, are responsible for the more positive outcomes. In addition, novel therapeutic methods and devices that await proof of cost effectiveness contribute to the ever-increasing costs of managing these patients. Unfortunately, many health care systems have limited interest in the most affected category of patients, the elderly population, who generally accounts for the most difficult diagnosis, monitoring, and therapeutic control problems.

### Controversies regarding therapeutic steps in heart failure

The new European Society of Cardiology guidelines for the management of heart failure published in 2016 provide some new insights. First, the (rather late) categorization of heart failure as preserved, mid-range (a relatively important category of patients, with ejection fractions between 40% and 50%, who have been somewhat neglected until recently), or reduced ejection fraction. Second, a new organization of therapeutic measures, with a more coherent chronology, including, in our opinion, only a few inconsistencies.<sup>2</sup> There is an overt lack of evidence for a clear systolic function category, which affects the duration and quality of life, mainly of elderly people who are often excluded from multicenter clinical trials.

One inconsistency is in conditioning therapeutic steps. In our opinion, the correct administration of loop diuretics is as initial therapy for symptomatic cases of reduced ejection fraction heart failure. This is where a great number of mistakes occur in current therapy, since diuretics are often not used for symptomatic therapy alone, either at the beginning of medical treatment or during chronic administration. First, without correct volemic control, initiation of pathogenic “lifesaving” therapy is pointless; eg, the initial use of more than 40 mg iv push furosemide in cases of acute pulmonary edema or, in cases of severe systolic function impairment and concomitant decreased renal flow function, intermittent furosemide administration, despite current indications regarding continuous iv administration of doses up to 1,000 mg/day. Despite acute heart failure decompensation episodes, especially during chronic routine therapy, the erroneous practice of intermittent diuretic administration remains common. To obtain proper diuresis, after the correction of overloaded fluids, decreasing the active loop diuretic dose to

the minimum, and then administering it daily, is sufficient in the majority of cases. Intermittent administration can lead to treatment resistance and also major volumic and electrolyte variations. Elderly people are the most difficult group in which to obtain therapeutic control without a major effect on global hemodynamics; however, after volumic correction using loop diuretic treatment, beginning treatment with beta blockers (four molecules for which there are evidence-based trials) and ACEI (or ARB for intolerant patients), also with molecules for which there are evidence-based trials (we do not believe that class effect is appropriate, particularly for heart failure treatment) should be performed by up-titration of doses.<sup>6–10</sup> Unfortunately, in the majority of cases, titration not only lasts for more than 12–16 weeks, but for several years, without reaching recommended therapeutic targets in a considerable proportion of patients (maximum doses are correctly based on levels of catecholamine receptors in these patients). This is one of the most frequent causes of therapeutic failure, and it results from the lack of an objective opinion and defensive attitudes among physicians, rather than from actual intolerance of patients. The most affected category of patients, in terms of lack of titration of therapeutic doses, is elderly people, who are often diagnosed in the advanced stages of disease and treated with inefficient therapeutic doses.

Moreover, the association of an aldosterone receptor antagonist (ARA) (spironolactone or eplerenone) should not be restricted by a left ventricular ejection fraction of less than 35%, since reduced ejection fraction heart failure is defined as less than 40%, and should, therefore define the beginning of pathogenic therapy. Regarding left ventricular ejection fraction, it is difficult to imagine major progression after the initiation of diuretic, beta blocker, and ACEI/ARB therapy; therefore, addition of ARA should not be considered because of left ventricular ejection fraction, or additional misleading symptoms. The myocardium salvaging, antifibrotic, and pleiotropic effects of ARA are long-established, regardless of symptoms.<sup>11,12</sup> Of course, careful attention to blood electrolytes is mandatory, since hyperkalemia is relatively predictable.

To address minor patient responses to optimal doses of ACEI/ARB, a new therapeutic class, the angiotensin receptor neprilysin inhibitor represents important progress, in terms of concept and pharmacology.<sup>13</sup> Until recently, the impact of atrial natriuretic peptide function on volumic and electrolyte control during therapy was neglected. Trials that evaluated the impact of the neutral endopeptidase inhibitors/ACEI, omapatrilat and candoxatril, unfortunately failed to demonstrate significant benefits, partly because of poor administration

and trial design.<sup>14</sup> The addition of a neprilysin inhibitor to the angiotensin 1 receptor blocker in the sacubitril/valsartan molecule, demonstrated a clear advantage in this specific category of patients (when using optimal doses), compared with the evidence-based ACEI, enalapril.<sup>13</sup> The effect of another medication with important additive functions, the antidiuretic hormone inhibitor, tolvaptan, remains under consideration.<sup>15</sup> In addition to the overall lack of evidence regarding new therapeutic classes, findings regarding their use for elderly people remain inconsistent.

In contrast, some therapeutic classes have persisted in the guidelines, such as the association of hydralazine with sustained release form of nitrates, which is still indicated for Afro-Americans, in part because of the genetically determined reduced response to ACEI in this population.<sup>2</sup> The important secondary effects of this association introduce a problem in administration and can also have negative effects. For example, in elderly people the addition of nitrates often induces severe hypotension, thus its routine use is rare in current practice.

A great many questions are also raised by the administration of digoxin, except for patients with high/medium ventricular rate atrial fibrillation. For patients in sinus rhythm, particularly those who are elderly and have impaired renal function, digoxin administration may be problematic in the absence of digoxinemia and electrolyte determination, parameters that are not always available.<sup>16</sup> In this specific case, the addition of a beta-blocker may lead to fatal bradyarrhythmia, particularly if there is a possibility of digitalis overdose. Moreover, the hemodynamic benefits of digoxin remain controversial. Various registries have demonstrated an even greater vulnerability in elderly people, who are much more sensitive to bradyarrhythmia and sudden cardiac death than the general population.<sup>17</sup>

Regarding ventricular rate for patients in sinus rhythm, a number of dedicated studies have demonstrated an advantage of administering sinus node bradycardic agents that do not affect systemic hemodynamics, such as ivabradine.<sup>18</sup> Concerning the unsupervised administration of this medication together with a beta blocker, as recommended by the guidelines, a few things should be highlighted. First, lowering the heart rate to less than 70 bpm is not recommended for any patient, at any stage of disease. Heart rate remains a compound of global cardiac performance and hemodynamic compensatory status, particularly in patients with low cardiac output and significant hypoxemia; eg, those with acute hemodynamic decompensation.

Controlling ventricular rate in elderly people presenting with atrial fibrillation is a rather controversial topic.

Ventricular rate control becomes the main therapeutic goal, since myocardial and epicardial fibrosis and remodeling of the left atrium are installed and as a result, reaching and maintaining sinus rhythm in this specific category of patients is highly unlikely. Administering a combination of digoxin and a beta blocker may be a risky combination, as well as IC or III class antiarrhythmic agents, with great impact on the contractile function. It is more likely that the most appropriate dosage of beta blocker indicated for the treatment of heart failure may be the optimum therapeutic choice, with atrioventricular node ablation and single chamber pacemaker with upper lead placement as therapeutic options to be taken into account when higher ventricular rate is encountered. Nevertheless, for patients with every form of atrial fibrillation, anticoagulant treatment is indicated, since all patients have a  $CHA_2DS_2-VAS_c$  score  $>2$ . In our opinion, in the case of a HAS-BLED score  $>4$ , the most reasonable option for the anticoagulant treatment is represented by direct oral anticoagulants, often using a reduced dosage related to renal function and reduced body mass index.

Heart rate control should not be considered in isolation, but rather in close association with volumic and oxygen binding capacity control. Also, control of iron deficiency, even in the absence of overt anemia, and consecutive treatment with ferric carboxymaltose, can lead to important symptomatic improvement in patients with chronic heart failure.<sup>19,20</sup> In elderly people, iron deficiency is even more strongly related to reduced quality of life because of nutrition issues, and may also be associated with cardiovascular, and more specifically hemodynamic, causes of death. Mitochondrial and myofibrillar energetic support therapy (trimetazidine, COQ10, ranolazine, which also has some antiarrhythmic benefits and omega 3 fatty acids) are somewhat supportive complementary therapies.

The specific pharmacodynamic status and vulnerability, along with malnutrition, cachexia, and chronic hypoxia of these patients are making any pharmaco-chemical therapeutic intervention more likely to be followed by severe adverse events and in many cases, efficient dosages and pharmacokinetics have a wide spectrum of differences compared to younger patients. Moreover, mostly in underweight women, the differences related to thrombogenic and fibrinolytic active factors are leading to a different therapeutic approach. This is one of the main reasons why, lately, novel therapeutic options based on myofibrillar energetics rather than on hemodynamic impact, are emerging.

Finally, the administration of therapies that are frequently required for other reasons, such as anticoagulant treatment, require close monitoring, since, along with their beneficial

effects, they are also associated with increased risks, especially in elderly people.

Recently, some novel therapies have been developed that directly target cardiomyocyte function by improving mitochondrial function or stimulating mitochondrial biogenesis (epicatechin and resveratrol), as well as regulating agents of mitochondrial fatty acid oxidation (inhibitors of malonyl-CoA decarboxylase, Q coenzyme and its analogs, EPI-743, and idebenone), blockers of the mitochondrial permeability transition pore or inhibitors of the mitochondrial sodium-calcium-lithium exchanger (eg, CGP-37157) along with the cell-permeable peptide, MTP-131 (also referred to as elamipretide) and omecamtiv mecarbil (CK-1827452), an agent that increases the calcium sensitivity of myofilaments.<sup>21</sup> Given the nature of their pathology and age-related features, elderly people may benefit from these treatments to a much greater extent. Finally, the administration of therapies that are frequently required for other reasons, such as anticoagulant treatment, require close monitoring, since, along with their beneficial effects, they are also associated with increased risks in elderly people.

In the future, progress in heart failure therapeutics is expected from replacing myofibrillar devitalized tissue therapy and stem cell therapy, both with positive experimental results so far.<sup>22</sup>

## Controversies regarding device therapy for heart failure and acute heart failure

The important role of cardiac resynchronization therapy for patients with specific indications related to left ventricular ejection fraction, electric pattern, and echocardiographic features (including speckle-tracking technique) is undeniable.<sup>23,24</sup> In contrast, the indications for fitting an implantable cardiac defibrillator, for primary prevention of sudden cardiac death, have recently been questioned by two well-designed studies including significant numbers of patients.<sup>25</sup> Although the secondary prevention of sudden cardiac death is clearly desirable, in reality this therapeutic approach may be excessive and can generate considerable discomfort in patients. The temporary use of a left ventricular assist device or biventricular assist device is an extreme indication (bridge to transplant); nevertheless, the use of this expensive therapy, or cardiac transplant, has not had a major impact on mortality rates, and addresses only a very restricted category of patients. Furthermore, devices that are increasingly efficient, making use of linear, rather than pulsatile pumps, without the need for anticoagulation,

can be important; however, they also raise issues regarding aseptic maintenance, pose a high risk of infection, and suffer mechanical wear. Unfortunately, elderly people are more likely to be excluded from such extreme therapeutic protocols, often for subjective reasons.

The current advantage of complete coronary revascularization for patients with ischemic heart disease, along with percutaneous valvular replacement procedures (transcatheter aortic valve implantation and over 100 reported cases of percutaneous mitral valve replacement procedures) may also be beneficial for patients with a life expectancy over 1 year; however, these raise questions of cost efficiency. In this case, elderly people are the recipients of these procedures which represent new opportunities for increased survival and life expectancy.

Because of severe remodeling and chamber dilatation, a process that also affects the mitral annulus, many elderly patients may have significant mitral regurgitation, with major impact on the left ventricular systolic function, generating frequent heart failure decompensation episodes. Sometimes, less extensive procedures compared to classic mitral percutaneous or surgical procedures, such as MitraClip, may provide significant benefit, as well as correction of other frequent valvular lesions in elderly patients – calcific aortic stenosis, with procedures such as TAVI (transcatheter aortic valve implantation) being more and more frequent. For elderly patients' valvular pathology specifically, the simple use of vasodilators and diuretics is not only useless but may also be harmful, with an aggressive therapeutic impact.

Beyond this technical progress, which is raising the cost of therapy for heart failure, more careful monitoring of patient progress, via clinical and paraclinical control visits, both within medical facilities and at home, would have a greater impact and be less expensive. For elderly people in particular, these specific measures may be both cost-efficient and beneficial in terms of increasing life expectancy. Telemetry remains expensive and is also unrealistic for many health care systems; however, monitoring of patients using specialized nurses is likely to be more efficient and accessible.

All disease registries have highlighted the fact that every new hospital admission for decompensated heart failure contributes to reducing the patient's life expectancy, by destruction of myocardial mass, caused by raised cardiac troponin levels commonly observed in episodes of acute pulmonary edema. Opportunistic treatment with vasopressor agents (epinephrine, norepinephrine), inotropes amines (dopamine, dobutamine), or even treatment with phosphodiesterase inhibitors (milrinone, enoximone, vesnarinone),

only increases the amount of compromised myocardium and the potential for fatal ventricular arrhythmia, when used in a prolonged and improper manner. These therapeutic measures should only be used in cases of profound hypovolemic shock and for a limited period of time. The situation differs slightly when these agents are administered in dilator or inodilator doses, and for a limited amount of time. The contribution of intra-aortic balloon pumps, in favor of invasive cardiology, for treatment of acute heart failure during acute myocardial infarction remains questionable, although long-term effects are unlikely. Also, it appears that arrhythmogenic risk overrides the advantages of these approaches for elderly people. Percutaneously implanted devices, such as the Impella (2.5 L/min or 5 L/min), are more efficient; however, they also raise the cost of procedures and, in the majority of cases, are only a transient solution until cardiac transplantation is possible.

Alternative inotropic/volemic therapies, such as levosimendan or nesiritide, are prohibited during acute myocardial infarction; however, they may be administered (no more than every 6 months), with the same risk of myocardial impairment and a more specific increased risk of arrhythmia, in patients with severely altered hemodynamic status. The same age-related reservations regarding the use of these types of interventions make their use problematic in elderly people.

## Conclusion

In conclusion, in our opinion, the greatest available benefits are not from drastic intermittent therapies, but can rather be achieved by very close general monitoring of patients with heart failure, including their diet, weight (the most critical category of heart failure patients are those who are underweight), salt and protein intake, mineral, vitamin, and nutrient intake, hydration, control of opportunistic infections (eg, pneumococcal vaccine), daily temperature monitoring, control and prevention of episodes of anxiety and depression (which are frequently observed in these patients with poor prognosis), close monitoring of medication, including antiplatelet, anticoagulant, non-steroid or steroid anti-inflammatories, antidepressants, and antibiotics etc., as these factors can lead to fatal events. Of course, physical therapy, emotional and psychological wellbeing, and maintaining a positive state of mind, are major contributors to quality of life and life expectancy. Quality of life coefficients are essential for a correct evaluation of medical performance, in a more meaningful way than life expectancy parameters; however, unfortunately, for patients with severe impairment of left ventricular ejection fraction, these goals and therapeutic

procedures are still not properly administered by current health care systems. Elderly patients require an even more thorough and individualized therapeutic approach, since the attitude toward this specific category of patients is often a performance indicator, as well as a measure of the social and cultural morality of health care systems.

## Disclosure

The authors report no conflicts of interest in this work.

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