Consensus Statement on Acute and Advanced Heart Failure

COUNCIL ON HEART FAILURE

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Abbreviations

AA Aldosterone antagonist
MCA Mechanical circulatory assistance
ARB Angiotensin II receptor blocker
MV Mechanical ventilation
LVAD Left ventricular assist device
BB Beta blockers
IABP Intraaortic balloon pump
ICD Implantable cardioverter defibrillator
FC Functional class
VSD Ventricular septal defect
CPAP Continuous positive airway pressure
CABGS Coronary artery bypass graft surgery
APE Acute pulmonary edema
ECG Electrocardiogram
EF Ejection fraction
AMI< Acute myocardial infarction
HF Heart failure
ACEI Angiotensin-converting enzyme inhibitor
MR Mitral regurgitation
IV Intravenous
NYHA New York Heart Association
SBP Systolic blood pressure
PCWP Pulmonary capillary wedge pressure
MVR Mitral valve replacement
ACS Acute coronary syndrome
HT Heart transplantation
CRT Cardiac resynchronization therapy
NIV Non-invasive ventilation
IPPV Intermittent positive pressure ventilation

[MTSAC] Full Member of the Argentine Society of Cardiology

BACKGROUND

During the XXXV Argentine Congress of Cardiology that took place in October 2009, the *Council on Heart Failure* of the Argentine Society of Cardiology presented the *Consensus Statement on Congestive Heart Failure;* the first part of it, Diagnosis and Treatment of Chronic Heart Failure, was published in the previous issue of the *Revista Argentina de Cardiología*. (1) We are now presenting the two most severe presentations of the disease, which offer the greatest challenge, due to the complexity and costs of heath care which depend mostly on costs related to hospitalization. This reality should not be ignored in our country, where mortality in patients hospitalized due to decompensated heart failure (HF) has not decreased in the last registries. (2)

This consensus statement has some differences with the first version of the *Consensus Statement on Heart Failure* published 10 years ago. (3) Although the *level of evidence A* is not enough to support the recommendations for the treatment of patients with decompensated acute or chronic heart failure, the experience and the outcomes of several studies have produced some changes in the management of patients hospitalized due to HF. On the other hand, few of the different electrophysiological and surgical procedures that have been incorporated for the treatment of advanced heart failure are supported by evidence. Although the indication of implantable cardioverter defibrillator and cardiac resynchronization therapy devices is not exclusive of advanced HF, we have chosen to include them in this chapter due to the level of complexity they require.

This Council has classified and ranked the usefulness or efficacy of the recommendations and the Level of Evidence as indicated in Tables 1 and 2.

It should be emphasized that the aim of this Consensus Statement is to guide physicians in the management of patients with acute or advanced heart failure and does not constitute a dogmatic rule that tries to replace the criterion of the attending physician in individual patient's care. Yet, the implementation of now recommendations may be affected by the availability of procedures and the experience of the environment where the patient is hospitalized. It would be expected that these recommendations might be modified in a near future by novel technological and pharmacological strategies and by the new evidence derived from new and ongoing clinical trials.

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CONSENSUS STATEMENT ON ACUTE HEART FAILURE

DEFINITION

Acute HF is defined as acute or gradual onset of symptoms or signs of HF that require urgent treatment. (4) The clinical characteristics of the disease are due to low cardiac output or tissue hypoperfusion, or to pulmonary or systemic congestion. Acute HF can present itself as acute de novo (new onset of acute heart failure in a patient without previously known cardiac dysfunction) or acute decompensation of chronic heart failure.

Several cardiovascular conditions (acute coronary syndromes, hypertension, valvular heart disease, arrhythmias, and pulmonary thromboembolism) or non-cardiac diseases (diabetes, anemia, and kidney failure) may be the causes and precipitating factors in acute HF.

EPIDEMIOLOGY

The prevalence of chronic HF and the number of hospitalizations due to decompensation have increased in the last years. Hospitalization consumes 75% of health care expenditure for the management of HF. Mortality during hospitalization is 4% - 8%, and is much greater in HF secondary to acute myocardial infarction (AMI) or cardiogenic shock. (2, 5, 6) About 35% to 50% of patients hospitalized with acute HF will be rehospitalized within the first year. The risk of death or rehospitalization varies from 25% to 35%. (2, 6, 7)

Different registries have defined simple clinical variables that have prognostic value; yet there are no

Table 1. Classification

– Clase I: condiciones para las cuales existe evidencia y/o acuerdo general en que el procedimiento o tratamiento es beneficioso, útil y efectivo. Una indicación de clase I no significa que el procedimiento sea el único aceptable.
– Clase II: condiciones para las cuales existe evidencia conflictiva y/o divergencias de opinión acerca de la utilidad/eficacia del procedimiento o tratamiento. - **Clase IIa:** el peso de la evidencia/opinión es a favor de la utilidad/eficacia. - **Clase IIb:** la utilidad/eficacia está menos establecida por la evidencia/opinión.
– Clase III: condiciones para las cuales existe evidencia y/o acuerdo general en que el procedimiento o tratamiento no es útil/efectivo y en algunos casos puede llegar a ser perjudicial.

Table 2. Level of Evidence

– Level of evidence A: consistent evidence from randomized clinical trials or meta-analyses. Multiple population risk strata evaluated. General consistency of direction and magnitude of effect.
– Level of evidence B: data derived from a single randomized trial, or non-randomized studies. Limited population risk strata evaluated.
– Level of evidence C: data derived from consensus opinion of experts, case studies, retrospective studies, registries.

models available for risk stratification. The ADHERE registry identified systolic blood pressure (SBP), urea and creatinine levels as predictors of in-hospital mortality. (5) The EuroHeart Survey on Heart Failure reported that advanced age, low SBP, coronary artery disease and kidney failure are associated with adverse in-hospital outcomes. (8) Recently, the last National Registry of Acute Heart Failure conducted by the SAC has identified leukocytosis and hyponatremia as variables associated with greater risk of morbidity and mortality. (2)

CLASSIFICATION

Acute HF may be classified according to clinical presentation in:

- **Acute *de novo* HF**: in the absence of chronic HF.
  - **Acute vascular failure:** increased peripheral resistance with or without systolic dysfunction.
  - **Acute myocardial failure:** transient or definite contractile dysfunction secondary to myocardial damage due to myocarditis, coronary event or other.
- **Decompensated chronic HF:** progression of chronic HF with signs or symptoms of HF which are mild and do not fulfill criteria for cardiogenic shock, or pulmonary edema.

Acute HF can also be classified from a clinical point of view according SBP values at admission, in **normotensive** (90-130 mm Hg), **hypertensive** (> 130 mm Hg) and **hypotensive** (< 90 mm Hg). (8)

EVALUATION AND DIAGNOSIS

The diagnosis of acute HF is based on symptoms and clinical data supported by the results of complementary tests. (9) The initial clinical evaluation should be safe and rapid. Clinical data obtained from physical examination provide an approach to patient's hemodynamic profile; thus, patients may be classified according to perfusion signs and symptoms (warm or cold) and on the presence or absence of congestion (dry or wet) (10):

- Group A: warm and dry;
- Group B: warm and wet;
- Group C: cold and wet;
- Group L: cold and dry.

These profiles have different prognosis and are useful to guide treatment in patients with decompensated chronic HF (Table 3).

Recommendations for the evaluation of acute HF

1. Clinical assessment of perfusion and congestion *(**Class I, level of evidence C**)*.
2. Evaluation of precipitating factors and comorbidities *(**Class I, level of evidence C**)*. Most episodes of acute HF are precipitated by factors that should be recognized so as not to fail in patient's management (Table 4).
3. The diagnosis should be supported by the results of laboratory and complementary tests. The **initial evaluation** should include plasma levels of creatinine, urea, electrolytes and troponin; complete blood count; electrocardiogram (ECG); chest x-ray and echocardiogram in the absence of recent data of ventricular function *(**Class I, level of evidence C**)*.

- **ECG:** gives information about heart rate, rhythm, conduction disturbances, and may orientate towards the etiology. Changes in the ST-T segment allow the diagnosis of acute coronary syndrome (ACS), and the presence of Q-waves indicates a history of MI. The ECG may also indicate hypertrophy or enlargement of cardiac chambers and changes suggestive of perimyocarditis. It is also useful to rule out the diagnosis of HF as only 10% of patients with systolic dysfunction have normal ECG.
- **Chest X-ray:** chest X-ray should be performed within one hour after admission to assess signs of pulmonary congestion (blood flow redistribution, bronchoalveolar infiltrates or pleural effusion), and the presence or absence of heart enlargement. Chest X-ray allows the evaluation of precipitating factors (pneumonia or pulmonary embolism).
- **Laboratory tests:** Table 5 describes the laboratory tests that should be performed. **Troponins** enable the identification of ACS as a cause or precipitating factor for acute decompensation; however, decompensation may also elevate troponins. **Arterial blood gas analysis** helps to the assessment of oxygenation, ventilation and acid–base balance. Measurement of arterial O_2 saturation with pulse oximetry can often replace arterial blood gases but not in very low output, vasocontricted shock states. Measurement of central venous O2 saturation and lactate levels may be useful for an estimation of the oxygen uptake in peripheral tissues. **Natriuretic peptides**, BNP and NT-proBNP, have high predictive value for the diagnosis of HF and are useful tools in the evaluation of patients admitted for dyspnea to the emergency department. However, in special situations, as during flash pulmonary edema (PE), BNP levels may remain normal at the time of admission. The result should be interpreted according to the clinical scenario. (11)
- **Doppler echocardiography:** Echocardiography is an essential tool for the evaluation of systolic and diastolic function, segmental wall motion abnormalities, pulmonary pressures, valvular heart disease, mechanical complications of AMI and pericardial diseases.

4. **Hemodynamic monitoring:** the insertion of a Swan-Ganz catheter for monitoring pulmonary pressures and cardiac pressure is not indicated in all patients. The use of a pulmonary artery catheter is recommended in those cases with a clinical profile difficult to identify, renal impairment despite favorable filling pressure, concomitant chronic obstruc-

Table 3. Hemodynamic profiles

Low perfusion	Congestion at rest	
	NO	SI
No	**A** Warm and dry	**B** Warm and wet
Sí	**L** Cold and dry	**C** Cold and wet

Vidence for congestion	Evidence for low perfusion
- High jugular venous pressure - Orthopnea - Edema - Liver enlargement - Ascites - Rales (rare in chronic patients) - S3 - Abdominojugular reflux	- Hypotension - Cold forearms and legs - May be sleepy, obtunded - Acute renal failure - Multiorgan failure

Table 4. Precipitating factors in AHF

–Decompensation of pre-existing chronic heart failure
-Surgeries
- Thyrotoxicosis
- Hypertension
- Renal dysfunction
– Anemia
- Arrhythmias
- Decompensation of respiratory diseases
– Shunts
- Lack of compliance with hygienic and dietetic measures
- Drug abuse
- Cardiac tamponade
- Volume overload
- Alcohol abuse
- Pulmonary embolism
- Infections
- Circulatory failure
- Hypertensive crisis
- Stroke
– Sepsis

tive pulmonary disease and cardiac conditions, or other situations that do not allow to make a precise diagnostic *(**Class IIb, level of evidence B**)*.

5. **Coronary angiography:** coronary angiography is indicated in patients with acute HF and evidence of ACS in the absence of contraindications *(**Class I, level of evidence B**)*.

TREATMENT

The goals of treatment are to stabilize the hemodynamic status and to improve symptoms as soon as possible without producing therapy-related side effects (hypotension, arrhythmias, hypovolemia and renal damage). The decision to admit a patient to a specific department and to indicate the initial therapy will depend on the hemodynamic status of the patient and the characteristics of the center.

Table 5. Laboratory tests in patients wit acute HF

Complete blood count	Always
Platelet count	Always
Urea and creatinine	Always
Electrolytes	Always
Blood glucose	Always
D-dimer	To be considered
Troponins and CK	Always
Arterial blood gases	In severe HF
Liver enzymes	To be considered
Plasma BNP or NT- pro BNP	To be considered

CK: Creatine kinase. BNP: B-type natriuretic peptide. NT-pro BNP: N-terminal pro b-type natriuretic peptide.

Recommendations for the treatment of acute HF

1. Treatment of patients requires a treatment plan in the hospital system including initial, follow-up and chronic therapy *(**Class I, level of evidence B**)*.
2. **Oxygen therapy:** O_2 should be administered as soon as possible in patient with hypoxemia to achieve O_2 saturation ≥ 95% (in patients with chronic obstructive pulmonary disease ≥ 90%) *(**Class I, level of evidence C**)*.
3. **Non-invasive ventilation (NIV):** between 8% and 30% of patients with cardiogenic APE need endotracheal intubation. These patients are severely compromised and endotracheal intubation is associated with a high rate of complications and mortality. Non-invasive ventilation has been used for more than 20 years in the treatment of APE to reduce the need of endotracheal intubation. In patients with acute HF, NIV improves loading conditions and increases cardiac output. (12) Small studies have compared traditional oxygen therapy

versus both modalities of NIV: continuous positive airway pressure (CPAP) and intermittent positive pressure ventilation (IPPV). (13, 14) The risk of AMI is greater with IPPV. (15) Some recent meta-analyses and studies have demonstrated that both methods reduce the need for endotracheal intubation between 50% and 60%; in addition, CPAP reduces mortality by 41% to 47%; however, there were no significant differences between both techniques. Recently, the 3CPO trial reported improvement in clinical parameters with absence of reduction in mortality. (16, 17)

The contraindications for NIV are respiratory arrest, hypotension (SBP < 90 mm Hg), lack of collaboration, inability to control secretions, impossibility of securing the mask, airway obstruction and cardiogenic shock. (18)

– NIV (CPAP or IPPV) should be indicated in patients with APE who do not require immediate endotracheal intubation in order to improve ventilatory and metabolic parameters *(**Class IIa, level of evidence B**)*.

4. **Morphine and its analogues:** morphine may be used intravenously (IV) in patients with acute HF associated with restlessness, anxiety, dyspnea or chest pain. Special care should be taken to use morphine and ventilatory parameters should be monitored. The initial dose is 2.5 to 5 mg; this dosing can be repeated if required *(**Class IIb, level of evidence C**)*.
5. **Intravenous diuretics:** Intravenous loop diuretics are widely used for the treatment of decompensated HF. (6) Most patients experience symptomatic relief secondary to fluid retention and diuretics are considered a standard of care. However, the use of these agents is based on empirical data. So far, there are no controlled, large-scale randomized clinical trials comparing the effects of diuretics with placebo due to the nature of this disease.

In the last years several publications have reported adverse events related with the use of diuretics. They include neurohormonal activation, especially of the angiotensin–aldosterone system, diuretic resistance due to hypertrophy of distal nephron and aggravation of renal failure. (19-21) High doses of intravenous loop diuretics during hospitalization have associated with worse in-hospital and long-term outcomes. (22) However, there is no consensus to define "high doses"; yet a cut-off value of 160mg/day of furosemide seems to divide populations with better and worse outcomes. (23) Although intensive treatment is clearly indicated in most compromised patients, it seems that the adverse effect related to high doses of diuretics is independent of the baseline conditions. (24) Part of this adverse effect is exerted on renal function. (25) Continuous infusion of furosemide is more effective than individual boluses, enhancing the excretion of sodium with less adverse effects. (26)

The association of loop diuretics with thiazides (hydrochlorotiazide 25 mg) and spironolactone (25-50 mg) improves the diuretic response reducing the adverse effects produced by high doses of furosemide in cases of diuretic resistance.

– Intravenous loop diuretics should be used in all patients hospitalized due to acute HF in the presence of symptoms secondary to congestion and fluid retention. SBP, electrolytes and renal function parameters should be careful monitored *(**Class I, level of evidence C**)*.
– Continuous IV infusion of loop diuretics should be given instead of boluses when high doses are required *(**Class IIa, level of evidence C**)*.

6. **Vasodilators:** vasodilators play a key role in the treatment of decompensated HF despite the lack of direct evidence showing reduction in mortality. They are indicated as first line therapy alone or in combination with diuretics. (26, 27) Special care should be taken at the moment of prescribing vasodilators only to patients with SBP > 90 mm Hg at admission and with clear evidence of volume overload. The association of two vasodilators should be avoided as it increases the risk of severe hypotension. The following vasodilators are the most frequently used:

– **Nitroglycerin:** it has a predominant venodilator effect, reducing left ventricular preload and relieving pulmonary congestion. Nitroglycerin is specially indicated in volume overload associated or produced by hypertension or ACS. The administration should be done with extreme caution by titration of the dose administered against blood pressure decrease. An arterial line should be inserted for blood pressure monitoring in case of hemodynamic instability. The use of nitroglycerin is mainly limited by the development of tolerance on continuous use. (27-30) Isosorbide dinitrate may be used sublingually before starting with definite intravenous treatment *(**Class IIa, level de evidence B**)*.
– **Sodium nitroprusside:** arterial and venous vasodilator that reduces both preload and afterload. (27, 28) Sodium nitroprusside should be titrated cautiously as it has a strong hypotensive effect. Placement of an arterial line is not an absolute indication; yet it may be considered. Prolonged administration may be associated with toxicity from thiocyanide, specially associated with renal failure, producing metabolic acidosis. Sodium nitroprusside is particularly useful in patients with acute HF associated with hypertension, severe mitral regurgitation and in cases with objective evidence of high peripheral resistance *(**Class IIa, level of evidence B**)*.
– **Neseritide:** Nesiritide is a recombinant human B-type natriuretic peptide with venous and arterial vasodilatory properties and diuretic and natriuretic effects. It can be administered by intravenous bolus or continuous infusion. Because of the longer half-life of nesiritide, hypotension can last longer than with other vasodilators. (27, 28, 31, 32) Some con-

troversial data has been reported about increased mortality and renal toxicity associated with neseritide; for this reason, new studies are reevaluating its indication. Renal function should be carefully monitored, and the initial bolus should be avoided in cases of borderline SBP (≤ 110 mm Hg) ***(Class IIb, level of evidence A)***.

Practical recommendations

Vasodilators should be considered first line therapy in acute HF secondary to or associated with hypertension. It is convenient to use them in combination with diuretics in order to enhance their effects and reduce the probability of adverse effects. Hypotension and renal function should be carefully controlled. The indications and doses of vasodilators are summarized in Table 6.

7. **Inotropic agents:** these drugs have limited indications in the treatment of decompensated HF. Inotropic support is clearly indicated as a temporary measure until improvement in the hemodynamic parameters is achieved. They are indicated in the presence of prolonged hypotension, peripheral hypoperfusion associated with congestion, progressive renal impairment, and as a bridge to ventricular support or heart transplantation in patients who are refractory to the initial treatment. The association with vasodilators increases the effectiveness of inotropic agents and reduces the duration of therapy with these drugs. The beneficial effects of an improvement in the hemodynamic parameters is, however, partially counteracted by the risks of long-term progression of myocardial dysfunction and supraventricular and ventricular arrhythmias that may lead to increased short and mid-term morbidity and mortality. (27, 28, 33, 34) Table 7 shows doses and routes of administration ***(Class IIb, level of evidence B)***.
   - **Dobutamine:** Dobutamine is a positive inotropic agent acting mainly through stimulation of beta receptors to produce dose-dependent positive inotropic and chronotropic effects. The initial dose of 2-3 µg/kg/min is progressively increased according to pressor and chronotropic responses. (34) Low doses of dobutamine produce pulmonary vasodilation. In patients receiving beta blockers (BBs), dobutamine doses have to be increased to displace the agonist from the receptor, thus increasing the risk of arrhythmias due to a predominant alpha effect ***(Class IIb, level of evidence C)***.
   - **Dopamine:** beta agonist. At low doses (2-3 µg/kg/min) dopamine acts only on renal dopaminergic receptors and produces vasodilation of the efferent arteriole, increasing diuresis with dissimilar results. (34, 35) At higher doses, dopamine acts on alpha-adrenergic receptors with increase in blood pressure and subsequent tachycardia and pro-arrhythmic events.

Table 6. Vasodilators used in acute HF

Vasodilator	Indication	Dose	Adverse effects
Nitroglicerina	APE-Pulmonary congestion with BP > 90 mm Hgg	Initial dose 10-20 µg/min, up to 200 µg/min,	Hypotension Headache Tolerance
Isosorbide dinitrate	APE-Pulmonary congestion with > 90 mm Hg	Initial: 5 mf SL, may repeat q20 min up to 40 mg/day	Hypotension Headache Tolerance
Sodium nitroprusside	APE-Pulmonary congestion with BP > 90 mm Hg	Initial: 0.3 µg/min, then slow titration ip to 5 µg/min	Hypotension Toxicity from thiocyanid Drug is light sensitive
Neseritide	Pulmonary congestion with SBP > 90 mm Hg	2 µg/min bolus+ 0,015-0,03 µg/kg/min* infusion	Hypotension Renal failure**

BP: Blood pressure. APE: Acute pulmonary edema.
*Bolus should be avoided with borderline BP.
**Results of the meta-analysis, under review.

Table 7. Inotropic agents used in acute HF

	Bolus	Infusion
Dobutamine	No	2-20 µg/kg/min
Dopamine	No	< 3 µg/kg/min renal effect 3-7 µg/kg/min inotropic effect; > 7 µg/kg/min pressor effect
Milrinone	25-75 µg/kg/min over 10-20 min	0.375-0.75 µg/kg/min
Levosimendan	12 µg/kg over 10 min (optional)	0,05-2 µg/kg/min (titration)
Norepinephrine	No	0.2-1.0 µg/kg/min

Dopamine is frequently used in combination with dobutamine *(**Class IIb, level of evidence C**)*.

– **Milrinone:** Milrinone is a type III phosphodiesterase inhibitor that increases cyclic AMP. This agent has inotropic and peripheral vasodilator effects. Milrinone increases cardiac output, produces pulmonary vasodilation and reduces pulmonary capillary wedge pressure (PCWP): As it does not stimulate beta-adrenergic receptors, milrinone maintains its effects even during concomitant beta blocker therapy. Milrinone is administered in IV bolus followed by continuous infusion. Hypotension and pro-arrhythmic events are the main adverse effects. Special care should be taken in patients with coronary heart disease as it may increase mortality (36-38) *(**Class IIb, level of evidence B**)*.
– **Levosimendan:** levosimendan acts through calcium sensitization of troponin C and produces peripheral and pulmonary vasodilation via ATP sensitive-potassium channel opening. Levosimendan infusion increases cardiac output and stroke volume, produces peripheral and pulmonary vasodilation and a decline in PCWP. Levosimendan is generally administered as a continuous intravenous infusion. Its hemodynamic effects may last around ten days. Hypotension and pro-arrhythmic events are the main adverse effects. As it does not exert its positive inotropic effects via beta-adrenergic receptors, it may be associated with beta blockers (39, 40) *(**Class IIb, level of evidence B**)*.
– **Norepinephrine:** norepinephrine is a vasopressor rather than an inotropic agent. It stimulates alpha-adrenergic receptors. Norepinephrine is not a first-line therapy drug and is indicated only in patients with cardiogenic shock refractory to treatment with inotropic agents and volume expansion in order to improve blood pressure and peripheral perfusion, generally as a bridge to coronary revascularization therapy. Other indications are septic shock associated with or as a cause of decompensated HF and vasoplegic syndrome following cardiac surgery (27, 28) *(**Class IIb, level of evidence C**)*.

8. **Digoxin:** digoxin is the cardiac glycosid most frequently used. Digoxin is indicated only in acute HF due to atrial fibrillation with high ventricular response for heart rate control (27, 28) *(**Class IIb, level of evidence**)*.

IMPLEMENTATION OF CHRONIC TREATMENT

Figure 1 summarizes management of acute HF during hospitalization.

Once clinical and hemodynamic stabilization has been achieved, the following measures should be implemented before and immediately after discharge:

1. Treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) and aldosterone antagonists (AAs) should be initiated before discharge according to the individual characteristics of each patient.
2. Explain to the patient and relatives the presence of alarming signs and symptoms to avoid rehospitalizations. Provide information about the disease in order to increase adherence to medical treatment and to hygienic and dietetic measures.
3. If possible, patients should be referred to HF management programs, especially in cases of advanced heart failure or multiple rehospitalizations (27, 28) *(**Class IIa, level of evidence B**)*.

CONSENSUS STATEMENT ON ADVANCED HEART FAILURE

DEFINITION AND IMPLICATIONS

Advanced HF is defined as persistence of limiting symptoms in New York Heart Association (NYHA) functional class (FC) III-IV despite complete and optimal therapy with agents of proven efficacy (diuretics, BBs, ACEIs/ARBs and AAs) in a patient with severe left ventricular dysfunction. (1) Optimal medical therapy applies to all treatment options defined for stages A, B and C with the addition of other interventions in refractory patients, as mechanical circulatory assistance (MCA), heart transplantation (HT) or other surgical options. Advanced HF is associated with high mortality (> 35% within one year), increased rehospitalization rate (> 60%after one year), physical disability and high costs, constituting a critical scenario.

As progression from stage C to D is sometimes difficult to define, in some cases there is a delay at the moment of prescribing more specific therapies or referring patients to tertiary care centers before the situation becomes irreversible. Before considering a patient refractory to treatment, it is important to search for potentially reversible factors that may lead to repeated rehospitalizations or LV dysfunction (Table 8). Several factors have been identified with adverse outcomes (Table 9).

The potential therapeutic options for the treatment of advanced HF include pharmacological treatment and palliative care of terminally ill patients, MCA, HT and other surgical approaches and device implant, such as cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillators (ICD). Although some of the indications of these devices are not exclusive of advanced HF, we have chosen to include them in this section due to the level of complexity they require.

MEDICAL TREATMENT

Recommendations for medical treatment in patients with advanced heart failure

Clase I

- Referral of patients to centers with expertise in the management of advanced HF is useful (28) *(**Level of evidence A**)*.

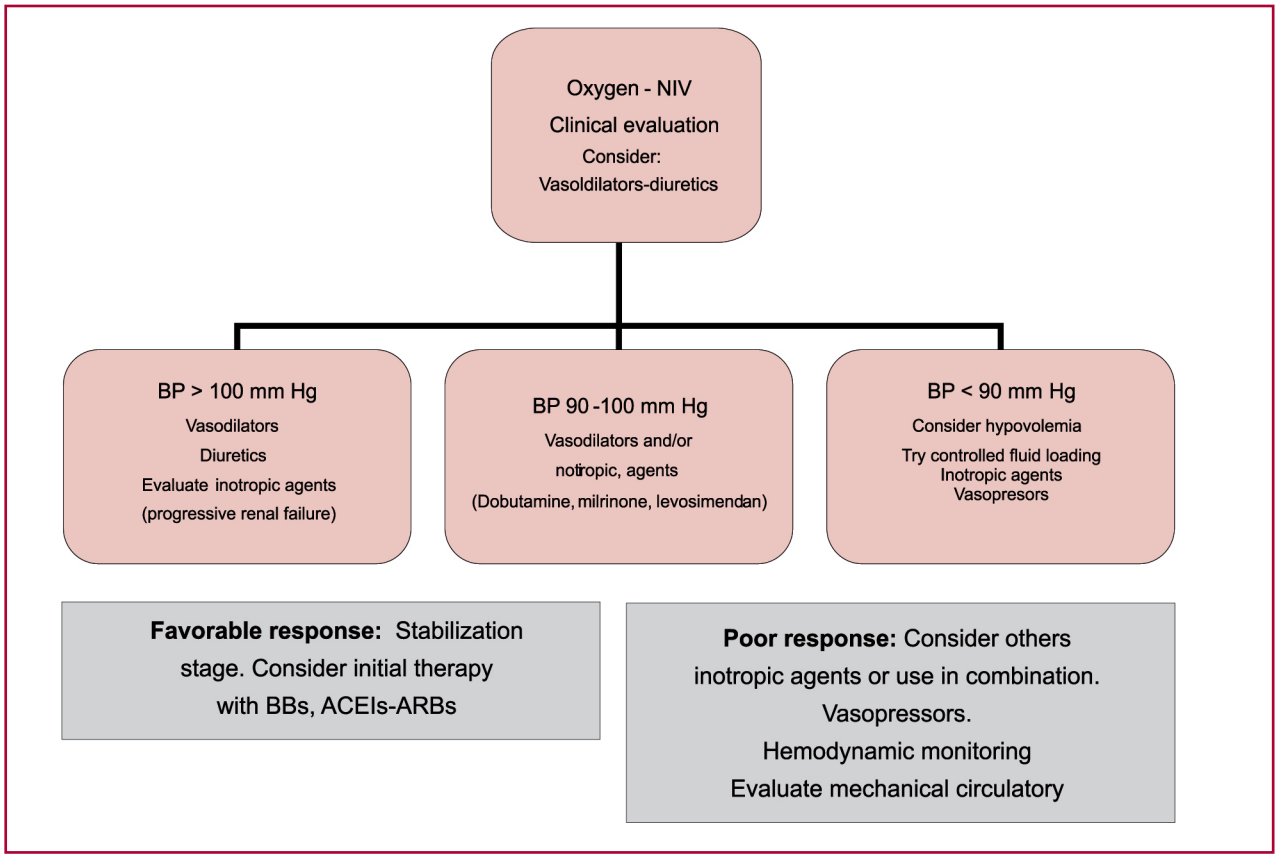

Fig. 1. Management of acute HF in hospitalized patients

Table 8. Decompensating factors in advanced HF

– Lack of compliance with diet or medical treatment
– Coronary events
– Supraventricular or ventricular arrhythmias
– Infections
– Pulmonary embolism
– Non-steroid anti-inflammatory drugs
– Use of negative inotropic agents (e. g., diltiazem, verapamil)
– Drug or alcohol abuse

Table 9. Predictors of poor outcomes in advanced HF

– Moderate to severe renal failure
– Intolerance to therapy with BBs and/or ACEIs
– Impossibility or absence of response to CRT
– Diuretics dose > 1.5 mg/kg/day
– Multiple rehospitalizations

BB: Betablocker. ACEI: Angiotensin-converting enzyme inhibitor.

- Medical treatment recommended for patients with symptomatic systolic dysfunction is also indicated for patients with severe HF. This includes general measures and pharmacological treatment with ACEIs, BBs, and AAs (1) ***(Level of evidence A)***.
- The use of ARBs is recommended in patients who do not tolerate ACEIs ***(Level of evidence B)***.
- Digoxin is recommended in patients with atrial fibrillation (1) ***(Level of evidence C)***.
- Meticulous identification and control of fluid retention is recommended in patients with refractory endstage HF (27, 28) ***(Level of evidence B)***.
- Continuous intravenous infusion of a positive inotropic agent may be considered as a bridge to other beneficial interventions: MCA; intraaortic balloon pump (IABP), angioplasty or coronary artery bypass graft surgery (CABGS) ***(Level of evidence C)***.
- Options for end-of-life care should be discussed with the patient and family when severe symptoms in patients with refractory end-stage HF persist despite application of all recommended therapies ***(Level of evidence C)***.

Class IIa

- Digoxin is recommended in patients with sinus rhythm and persistent symptoms despite optimal medical treatment (1) ***(Level of evidence B)***.
- In patients with diuretic resistance, ultrafiltration may be needed to achieve adequate control of fluid retention (27, 28) ***(Level of evidence B)***.
- Circulatory assistance with IABP or complex MCA, ultrafiltration or hemofiltration may be used as a bridge to HT ***(Level of evidence C)***.
- Continuous intravenous infusion of a positive inotropic agent may be considered for palliation of

symptoms in patients with refractory end-stage HF *(**Level of evidence C**)*.
- Referral of patients with refractory end-stage HF to an HF program with expertise in the management of refractory HF is useful to optimize quality care and adhesion to treatment in order to improve the clinical outcomes and prognosis, reduce hospitalizations and health costs (1, 41) *(**Level of evidence B**)*.

Class IIb
- Pulmonary artery catheter placement may be reasonable to guide therapy in patients with refractory endstage HF and persistently severe symptoms *(**Level of evidence C**)*.
- Patients with signs and symptoms of cardiac cachexia may benefit from high calorie intake, anabolic therapy or appetite stimulants *(**Level of evidence C**)*.

Class III
- Routine intermittent infusions of positive inotropic agents are not recommended for patients with refractory end-stage HF *(**Level of evidence B**)*.

PALLIATIVE TREATMENT

Palliative care is applicable to all patients with HF, but especially to those with refractory endstage HF with poor prognosis (survival < 12 months). All professionals working with HF patients should examine current end-of-life processes and work towards improvement in approaches to palliation and end-of-life care. In occasions it seems reasonable to let the patient take the initiative to raise his/her doubts; however, it is useful to talk with the patient and relatives about the prognosis, expectations and preferences according to the patient's educational level and cultural patterns.

Pharmacological and non pharmacological therapies should focus on achieving the best quality of life possible. Drugs which modulate the effects of neurohormonal activation (BBs, ACEIs, AAs) improve symptoms and should not be withdrawn; doses should be adjusted according to blood pressure and functional class.

When no therapy will modify the course of the disease, succumbing to a sudden death instead of dyspnea due to congestion may be a better mode of dying. In this scenario patients should have their ICD inactivated.

Recommendations for patients with refractory endstage HF

Class I, Level of evidence C
- Palliative care measures should be considered and adopted.
- Ongoing patient and family education regarding prognosis for functional capacity and survival is recommended.

Class IIa, Level of evidence
- Implementation of measures that are appropriate to the relief of suffering, including opiates, inotropes and intravenous diuretics for symptom palliation are recommended.
- Discussion is recommended regarding the option of inactivating ICDs for patients with HF at the end of life.

Class III, Level of evidence C
- Aggressive procedures performed within the final days of life (including intubation and implantation of ICD in patients with NYHA functional class IV symptoms who are not anticipated to experience clinical improvement from available treatments) are not appropriate.

MECHANICAL CIRCULATORY ASSISTANCE

Mechanical circulatory assistance is indicated in patients with refractory HF with requirement of continuous IV infusion of inotropic agents with severe hemodynamic impairment: PCWP < 20 mm Hg, cardiac index < 2 L/min/m^2 and SBP < 80 mm Hg. There are two modalities of MCA: short- or long-term mechanical support. Intraaortic balloon pump is one of the most frequently circulatory support devices used as short-term treatment. Complex MCA may be used as a bridge to transplantation, myocardial recovery or long-term support in patients who are not heart transplantation candidates. (42)

Intraaortic balloon pump (IABP)

Intraaotic balloon pump reduces left ventricular afterload and improves myocardial O_2 supply/demand ratio associated with slight increase in systemic perfusion. Intra-aortic balloon pump is recommended when cardiogenic shock is not quickly reversed with pharmacological therapy when a potentially reversible cause of shock can be established or in case of feasibility of HT or other therapeutic option. In patients with advanced HF refractory to therapy with two inotropic agents or with malignant ventricular arrhythmias, IABP is used as a bridge to HT.

Recommendations for IABP in patients with acute or advanced HF

Class I
- Cardiogenic shock due to MI associated with a reperfusion strategy *(**Level of evidence B**)*.
- Ventricular septal defect (VSD) or severe mitral regurgitation (MR) due to MI *(**Level of evidence B**)*.
- Cardiogenic shock not quickly reversed with pharmacological therapy or in case of feasibility of HT *(**Level of evidence C**)*.

Class IIa
- Refractory HF when there is the potential for myocardial recovery (bridge to recovery) in the absence of complex devices *(**Level of evidence C**)*.

Class IIb

- IABP is recommended as a bridge to surgical approach or other type of complex long-term MCA *(**Level of evidence C**)*.

Class III

- Refractory cardiogenic shock in the absence of a potential cause for myocardial recovery *(**Level of evidence C**)*.
- Aortic regurgitation, aortic dissection or severe aortoiliac disease *(**Level of evidence B**)*.

Mechanical circulatory assistance with more complex devices

Ventricular assist devices (VADs) are useful for most patients with advanced HF, even with biventricular impairment. These complex devices are most frequently used as a bridge for HT in candidates with severe circulatory failure. This indication represents 80% of implants. They are rarely used as an alternative to transplant or as a bridge to recovery.

The features of these devices allow long-term use, particularly in no transplant candidates with severe HF. The REMATCH trial included no transplant candidates with more severe disease at baseline than did patients in other randomized trials of treatment for heart failure. Long-term support with a left ventricular assist device resulted in substantial improvement in survival. Mortality decreased from 76% to 51% in patients treated with IV inotropic agents, but a few patients survived after two years. (43)

The use of these devices in our environment is limited due to their high costs; in this way, these recommendations apply only to tertiary care centers with trained staff for management of these devices.

Recommendations for CMA with more complex devices

Class I

- For patients with severe refractory HF despite maximal inotropic support and /or IABP (IC < 2 ml/kg/min and PCWO > 20 mm Hg), as a bridge to HT *(**Level of evidence C**)*.

Class IIa

- For patients with severe acute myocarditis, as a bridge to myocardial recovery *(**Level of evidence C**)*.

Class IIb

- Consideration of an LV assist device is reasonable in highly selected patients with refractory end-stage HF and an estimated 1-year mortality over 50% with medical therapy, contraindications to HT or no transplant candidates (43) *(**Level of evidence B**)*.

Class III

- Patients with advanced HF without optimal treatment *(**Level of evidence C**)*.
- Severe systemic diseases, as severe multiorgan disease, uncontrolled sepsis, liver cirrhosis with portal hypertension and heparin-induced thrombocytopenia *(**Level of evidence C**)*.
- Active psychosis *(**Level of evidence C**)*.
- Permanent hemodialysis *(**Level of evidence C**)*.
- Inappropriate body size for the available VAD *(**Level of evidence C**)*.

HEART TRANSPLANTATION

Patients with severe HF despite optimal pharmacological therapy in the absence of other alternative treatment and with HF known to have poor outcomes should be considered for HT. Despite the absence of controlled trials, the experience has demonstrated the HT is a therapeutic option for patients with advanced endstage HF that increases survival, exercise capacity and quality of life. Survival after 1 and 10 years is 80% and 50-60%, respectively, when HT is performed according to the published evidence. The most common causes of mortality during the first year are primary graft failure and multiorgan failure, followed by graft rejection and infection. Graft vascular disease and neoplasms are the main causes of long-term mortality. (44)

Unfortunately, most patients cannot expect transplantation due to shortage of donors. For this reason, selection of eligible patients should be very strict in order to identify those patients with worse prognosis that might obtain the best benefit from HT. Reversible diseases and conditions with other medical or surgical options should be ruled out before submitting a patient to HT.

Patients in cardiogenic shock with requirement of IV drugs, mechanical ventilation (MV) and/or MCA constitute the group with greatest mortality in the short-term and are considered candidates for HT. In addition, patients with advanced HF and severe left ventricular dysfunction with frequent episodes of decompensated HF and FC III-IV despite optimal medical treatment should also be considered for HT. Those patients with greatest risk of 1-year mortality should be selected from this population using different prognostic markers. Table 10 shows the clinical conditions that increase morbidity and mortality after transplantation that have been defined by the International Society for Heart & Lung Transplantation (ISHLT) as absolute and relative contraindications (45) Chagas cardiomyopathy, a common disease in our environment, is not currently a contraindication for HT. (46)

Recommendations for HT in patients with HF

Class I

- Patients with advanced HF with dependence on IV drugs, NV and/or MCA *(**Level of evidence C**)*.
- Patients with advanced HF and high 1-year mortality (> 30%) estimated by clinical markers despite

Table 10. Contraindications to heart transplantation

Absolute contraindications
– Active sepsis
– Malignancy with high risk of recurrence
– Drug and alcohol abuse
– Active psychosis
– HIV infection
– Documented nonadherence or inability to comply with medical therapy
Relative contraindications
– Age > 70 years
– Pulmonary hypertension (PVR > 6 UW or transpulmonary gradient > 16 mm Hg). If PVR decreases to < 2.5 UW with vasodilators but PSP decreases below 85 mm Hg, the patient is at high risk of right ventricular failure and postoperative mortality
– Severe cerebrovascular disease and peripheral artery disease with limiting symptoms, not amenable to revascularization, with limitations to rehabilitation
– Renal dysfunction (creatinine clearance < 40 ml/h). The indication of combined heart-kydney transplant should be considered
– Obesity (body mass index > 30 and ideal body weight percentage > 140%)
– Diabetes with target organ lesion, with the exception of nonproliferative retinopathy, and poor glycemic control (HbA1c > 75)
– Recent pulmonary infarction
– Psychiatric disorders
– Absence of a consistent or reliable social support system
– Abstinence from smoking < 6 months

HIV: Human immunodefficiency virus. PVR: Pulmonary vascular resistance. SBP: Systolic blood pressure.

optimal and adjusted medical treatment *(**Level of evidence C**)*.

- Patients with advanced HF with peak O_2 uptake < 10 ml/kg/min (47) *(**Level of evidence C**)*.
- Patients with HF and severe, symptomatic ventricular arrhythmias unresponsive to antiarrhythmic therapy and ICD *(**Level of evidence C**)*.

Class IIa

- Patients with advanced HF with peak O_2 uptake between 11 and 14 ml/kg/min who do not tolerate BBs (47, 48) *(**Level of evidence B**)*.
- Cardiogenic shock with multiorgan failure potentially reversible *(**Level of evidence C**)*.

Class IIb

- In patients with HF with peak O_2 uptake between 11 and 14 ml/kg/min who tolerate BBs it is recommended to evaluate the risk score for prognosis stratification (47, 49) *(**Level of evidence C**)*.
- Patients with indication for HT and relative contraindications *(**Level of evidence C**)*.

Class III

- Patients with HF under incomplete medical treatment *(**Level of evidence C**)*.
- Patients with HF who are candidates for other corrective surgical or interventional procedure *(**Level of evidence C**)*.
- Patients with absolute contraindications for HT *(**Level of evidence C**)*.

SURGICAL OPTIONS

The demand for donors for HT is currently greater than their supply; for this reason, surgical options are important as they do not require donors and their results are comparable to those of transplantation. In patients with advanced HF, CABGS, surgical correction of MR and ventricular reconstruction techniques are the most common surgical approaches. Dynamic cardiomyoplasty and aortomyoplasty with skeletal muscle (50, 51), and implant of Acorn or Myosplint devices try to limit ventricular dilation and reduce myocardial V O_2; however, the experience with these procedures is limited.

Cell therapy with myoblasts or bone marrow-derived stem cells is currently under clinical investigation, with promising results. (52-54)

Coronary artery bypass graft surgery

Heart failure due to coronary artery disease is the consequence of ventricular dysfunction associated with chronic ischemia, acute and reversible systolic/diastolic dysfunction, mechanical complications of MI (MR, ventricular rupture, VSD, ventricular aneurysm) or a combination of all these conditions. Stunning and hibernation are the major components of chronic ventricular dysfunction. The evidence indicates that revascularization of stunning myocardial area produces recovery of ventricular function over the time. (55)

In patients with ventricular dysfunction and HF, CABGS is indicated in the presence of angina or documented evidence of myocardial viability/ischemia in ECG (absence of Q waves in coronary artery territories with wall motion abnormalities), perfusion scintigraphy, echocardiography, magnetic resonance imaging or positron emission tomography. (1)

In patients with ischemic cardiomyopathy without documented evidence of myocardial viability, CABGS does not produce any benefit. On the other hand, CABGS may be a valid option in patients with severe left ventricular dysfunction and area of viable myocardium > 20% with suitable coronary artery anatomy. (56) In certain cases, surgery may be performed with cardiopulmonary bypass or with IABP which reduce the risk of complications. Percutaneous coronary interventions are also a possibility with lower risk for the patient.

Recommendations for CABGS in advanced HF

The following recommendations should be applied only in cases of significant viability (ischemia or hibernation) and coronary arteries suitable for revascularization.

Class I

- Patients with poor LV function who have significant left main coronary artery stenosis *(**Level of evidence B**)*.
- Patients with poor LV function who have left main equivalent: significant stenosis of the proximal LAD and proximal left circumflex artery *(**Level of evidence B**)*.
- Patients with poor LV function who have proximal LAD stenosis with 2- or 3-vessel disease *(**Level of evidence B**)*.

Class IIa

- Patients with poor LV function with significant viable noncontracting, revascularizable myocardium and without any of the above anatomic patterns *(**Level of evidence B**)*.
- Patients with acute HF and known or suspected coronary artery disease in whom coronary angiography with subsequent revascularization is a reasonable indication for improving patients' survival *(**Level of evidence C**)*.

Class IIb

- Transmyocardial laser revascularization as an isolated therapy or as a complement to CABGS might be used in patients with angina refractory to medical therapy and who are unsuitable for surgical revascularization or PCI (56) *(**Level of evidence B**)*.

Class III

- CABG should not be performed in patients with poor LV function without angina or evidence of ischemia and without evidence of significant revascularizable viable myocardium *(**Level of evidence B**)*.

Mitral regurgitation surgery

Mitral regurgitation surgery is recommended in symptomatic patients with evidence of systolic dysfunction (EF < 0.60 and/or end-systolic diameter > 40 mm). It is difficult to determine which patients with symptomatic MR and advanced left ventricular dysfunction are candidates for surgery. Indeed, the question is which patient is not currently eligible for surgery. In addition, primary cardiomyopathy with secondary mitral regurgitation is difficult to distinguish from primary regurgitation as a cause of dilated cardiomyopathy. (57, 58) Mitral valve repair should be always considered regardless of the etiological discussion. This procedure is the operation of choice when the valve is suitable for repair in all patients with severe MR. (59, 60) Mitral valve replacement (MVR) should be performed with preservation of the subvalvular apparatus and ventricular architecture.

Recommendations for MR surgery in patients with advanced HF

Class IIa

- MV surgery is reasonable for patients with chronic severe MR due to a primary abnormality of the mitral apparatus and NYHA functional class III–IV symptoms and severe LV dysfunction (ejection fraction less than 0.30 and/or end-systolic dimension greater than 55 mm) in whom MV repair is highly likely *(**Level of evidence C**)*.
- MVR with preservation of the subvalvular apparatus is reasonable for patients with chronic severe MR due to a primary abnormality of the mitral apparatus and NYHA functional class III–IV symptoms and severe LV dysfunction (ejection fraction less than 0.30 and/or end-systolic dimension greater than 55 mm) in whom MV repair is not likely *(**Level of evidence C**)*.
- MV repair or MVR with preservation of the subvalvular apparatus may be considered for patients with chronic severe secondary (functional) MR due to severe LV dysfunction (ejection fraction less than 0.30) who have persistent NYHA functional class III–IV symptoms despite optimal therapy for HF *(**Level of evidence C**)*.

Class IIb

- The effectiveness of mitral valve repair or MVR has not yet been established for severe secondary (functional) MR, severe LV dysfunction and end-stage refractory HF (60) *(**Level of evidence C**)*.

Surgical ventricular reconstruction

The aim of these procedures is to reduce and restore ventricular geometry excluding akinetic wall areas. In consequence, wall stress and myocardial O_2 uptake decrease.

Ventricular aneurysmectomy is the first and most common of these techniques. **Dynamic cardiomyoplasty** provides biologic support with skeletal muscle. This technique has demonstrated clinical improvement in patients with FC III with absence of significant heart enlargement, MR or pulmonary hypertension; however, the lack of improvement in survival has limitd its use. (50, 51) Despite partial **left ventriculectomy** (also known as Batista operation) was believed to be a promising therapeutic option for the treatment of advanced HF, it failed to provide clinical improvement and was associated with high postoperative mortality. (61)

Surgical ventricular restoration by means of the **Dor procedure** is a surgical option that may be used in combination with revascularization procedures and/or mitral valve repair. (62) The STICH (Surgical Treatment for Ischemic Heart Failure) trial enrolled patients with coronary artery disease and HF to address the question of whether surgical ventricular reconstruction added to CABGS would improve the outcomes as compared with CABGS alone or medical treatment. The study failed to demonstrate clinical improvement of CABGS with ventricular reconstruction compared to isolated revascularization. (63)

Recommendations for surgical ventricular reconstruction

Class I

- Ventricular aneurysmectomy is recommended in patients with H secondary to left ventricular aneurysm when the procedure is technically feasible *(**Level of evidence C**)*.

Class IIb

- Surgical ventricular reconstruction technique might be used in combination with CABGS and/or surgical correction of MR in selected patients with advanced HF, ventricular dilatation and extensive areas of necrosis when HT cannot be performed (63) *(**Level of evidence B**)*.

Class III

- Partial ventricular ventriculectomy (Batista operation) is not recommended in patients with dilated cardiomyopathy and HF *(**Level of evidence C**)*.

CARDIAC RESYNCHRONIZATION THERAPY

Conduction abnormalities and contraction dyssynchrony are common in patients with left ventricular dysfunction and HF. Several types of dyssynchronous activation are seen in heart failure, such as interventricular dyssynchrony (between both ventricles), interventricular dyssynchrony (in both ventricles) and atrioventricular dyssynchrony. Contraction dyssynchrony aggravates ventricular function increasing ventricular volumes and mitral regurgitation. (64)

The first physiopathological trials were followed by studies that included clinically relevant endpoints (mortality/rehospitalizations). Cardiac resynchronization therapy reduces average mortality by 22% and rehospitalizations due to HF by 37% in patients with severe ventricular dysfunction and advanced HF. (65-68) Reduction in mortality includes mortality due to progression of HF and sudden death. (69) Two recent trials, the MADIT-CRT and REVERSE, demonstrated that the device improves the clinical outcomes without changes in mortality in patients with severe left ventricular dysfunction, sinus rhythm, wide QRS complex and mild cardiac symptoms. (70, 71)

Approximately 30% of patients with indication of CRT present lack of favorable response. The lack of improvement with CRT can be due to many factors including incorrect selection of patients (absence of mechanical dyssynchrony), necrosis in the site of placement of the left lead, the placement of the left ventricular pacing lead in an inappropriate location, absence of pacemaker rhythm during long periods of time, etc. Some echocardiographic parameters of dyssynchrony have proved to be useful to identify responders to CRT in small studies; however, they need to be confirmed by large multicenter trials. Echocardiography should not be indicated for candidates' selection, and should only be used in cases of doubts. (72-74)

Indications for cardiac resynchronization therapy

Class I

- Patients with chronic HF with functional Class III - IV heart failure symptoms under optimal medical therapy, LVEF ≤ 35%, sinus rhythm and QRS duration ≥ 150 ms *(**Level of evidence A**)*.
- Patients with indication of permanent pacing or needing pacemaker upgrade, with chronic HF with FC III-IV symptoms (lasting for at least 6 months), under optimal medical therapy, EF < 35% *(**level of evidence B**)*.
- Patients with indication of CRT and ICD therapy (75-76):
  - For "secondary prevention": patients with indication of ICD (sustained ventricular tachycardia or sudden death) *(**Level of evidence A**)*.
  - For "primary prevention": CRT associated with ICD in young patients without severe comorbidities and expectation of survival > 2 years, especially in patients with a history of ventricular tachycardia *(**Level of evidence C**)*.

Class IIa

- Patients with chronic HF with functional Class III - IV heart failure symptoms (lasting for at least 6 months) under optimal medical therapy, LVEF ≤ 35%, sinus rhythm and QRS duration between 120 to150 ms. Parameters of mechanical dyssynchrony should be evaluated *(**Level of evidence B**)*.
- Patients with chronic HF with functional Class I - II heart failure symptoms under optimal medical therapy, LVEF ≤ 30%, sinus rhythm and QRS duration ≥ 150 ms *(**Level of evidence B**)*.

Class IIb

- Patients with chronic HF with functional Class III - IV heart failure symptoms (lasting for at least 6 months) under optimal medical therapy, LVEF ≤ 35%, atrial fibrillation and QRS duration ≥ 150 ms. Atrial fibrillation patients should develop pharmacological AV block or undergo AV-junctional ablation to ensure that most beats will be conducted by the CRT device *(**Level of evidence B**)*.
- Patients with indication of permanent pacing or needing pacemaker upgrade, with EF < 35% and absence of clinical evidence of HF. In pacemaker-dependent patients, CRT may be recommended *(**Level of evidence C**)*.

IMPLANTABLE CARDIOVERTER DEFIBRILLATOR THERAPY

Implantable cardioverter defibrillator therapy is currently the best tool to prevent sudden death. Indications for ICD therapy are classified into primary and secondary prevention strategies.

Secondary prevention

Secondary prevention indications are clear. The indication of an ICD device for secondary prevention has been well documented in three clinical trials and in a meta-analysis of these three trials. (77-80)

Recommendations for ICD therapy in secondary prevention

Class I

- ICD therapy is recommended for secondary prevention in patients who survived ventricular fibrillation or hemodinamically unstable ventricular tachycardia, or ventricular tachycardia with syncope and who have a LVEF ≤ 40%, who are receiving chronic optimal medical therapy and who have a reasonable expectation of survival with a good functional status for more than 1 year *(**Level of evidence A**)*. (77-80)

Primary prevention

Primary prevention indications for ICD therapy were analyzed by the MADIT II and SCD-HeFT trials. (76, 81) The MADIT II trial was conducted on patients with previous MI one month or more before entry, EF < 30% and FC I-III heart failure symptoms, and demonstrated 31% reduction in the risk of death at 20 months of follow-up. The SCD-HeFT trial enrolled patients with class II or III HF symptoms due to ischemic or idiopathic causes, and reported a reduction in the risk of death by 23 percent after 45 months. However, the DINAMIT study, which included patients with EF < 36% and previous MI 6 to 40 days before did not found significant differences in 30 month-mortality. Although ICD therapy was associated with a reduction in the rate of death due to sudden death, this effect was offset by a significant increase in the rate of death from HF in the control group. (82) Recently, the IRIS trial, which included patients who had suffered a MI 5 to 31 days before, EF < 40% and sinus tachycardia or ventricular arrhythmia, did not find significant differences at 3 years. (83)

How many persons should receive an ICD? Despite the lack of detailed information, the application of the inclusion criteria of the MADIT II and SCD-HeFT trials would place an economic burden difficult to support. According to this evidence, 17 patients should receive an ICD to prevent one death every two years or 14 patients should receive an ICD to prevent one death every four years. (76, 81) The effectiveness of the procedure should be optimized by an appropriate selection of patients. However, currently there are no specific tools to identify those patients at risk. For this reason, secondary prevention indication for ICD therapy in patients with HF was considered *class IIa*.

None of the studies demonstrated a significant reduction in mortality in the group of patients with ventricular dysfunction due to non ischemic causes in an individual analysis. (84-86) Yet, a meta-analysis of the three most important studies showed a significant reduction in mortality after ICD implant alone or associated with CRT in this population. (87)

Recommendations for ICD therapy in primary prevention

Class IIa

- ICD therapy is recommended in patients with HF due to prior MI who are at least 40 days post-MI, have an LVEF < 35%, are NYHA functional class II or III, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year *(**Level of evidence A**)*.
- ICD therapy is recommended in patients with idiopathic HF who have an LVEF < 35%, are NYHA functional class II or III receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year *(**Level of evidence B**)*.
- ICD therapy is recommended in patients with HF due to prior MI who are at least 40 days post-MI, have an LVEF < 30%, are NYHA functional class I (asymptomatic) receiving chronic optimal medical therapy, and who have a reasonable expectation of survival with a good functional status for more than 1 year *(**Level of evidence B**)*.

Class III

- ICD therapy is not recommended in patients with left ventricular dysfunction before 40 days post-MI *(**Level of evidence A**)*.

The magnitude of the studies and the results obtained suggest that there is enough evidence demonstrating reduction in mortality However, there are no reports of better physiopathological effects or improved quality of life, and the unquestionably high cost-effectiveness ratio has not been thoroughly studied in the different subgroups. Probably, a better individualization of patients at risk of sudden death might optimize the indication of ICD therapy.

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