Advanced circulatory support: artificial heart use in patients with heart failure

Suporte circulatório avançado: uso do coração artificial em pacientes com Insuficiência cardíaca

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ABSTRACT
Objectives: To analyze recent clinical trials about mechanical circulatory support and other adjuvant therapies for the treatment of heart failure. Methods: Articles were selected from the Pubmed and Embase databases published between the years 2015 and 2020, randomized controlled trial or not. The descriptors used were: assisted circulation AND artificial heart AND heart failure, and the descriptor artificial heart was not used for research at EMBASE with 2 articles as results. And 40 at PubMed with the filters: Controlled Clinical Trial, published in the last 5 years, Humans. Results: Several therapies have been proposed as management alternatives for critically ill patients with heart failure. Among them, we can highlight the HeartMate III implant, which has been shown to have fewer adverse effects compared to HeartMate II; the implantation of an atrial bypass device, which has been shown to decrease the pressure of pulmonary artery occlusion in 1 month compared to the control group, but has shown no long-term effects; and the use of mesenchymal precursor cells, which has not been shown to be significantly effective. Final considerations: It is suggested to carry out further studies to improve the indication criteria, making it possible to allocate resources in hospitalized patients.

Keywords: Circulatory Failure, Cardiac failure, Heart-Assist Devices
selecionados nas bases de dados Pubmed e Embase publicados entre os anos de 2015 e 2020, com ou sem ensaio clínico randomizado. Os descritores utilizados foram: circulação assistida E coração artificial E insuficiência cardíaca, e o descritor coração artificial não foi utilizado para pesquisa na EMBASE com 2 artigos como resultados. E 40 no PubMed com os filtros: Controlled Clinical Trial, publicado nos últimos 5 anos, Humans. Resultados: Diversas terapias têm sido propostas como alternativas de manejo para pacientes críticos com insuficiência cardíaca. Dentre eles, podemos destacar o implante HeartMate III, que demonstrou ter menos efeitos adversos em comparação ao HeartMate II; o implante de um dispositivo de bypass atrial, que demonstrou diminuir a pressão de oclusão da artéria pulmonar em 1 mês em comparação com o grupo controle, mas não mostrou efeitos em longo prazo; e o uso de células precursoras mesenquimais, que não se mostraram significativamente eficazes. Considerações finais: Sugere-se a realização de novos estudos para aprimorar os critérios de indicação, possibilitando a alocação de recursos em pacientes hospitalizados.

Palavras-chave: Insuficiência circulatória, insuficiência cardíaca, dispositivos de assistência cardíaca

1 INTRODUCTION

Heart failure (HF) is a complex clinical syndrome characterized by the inability of the heart to act as a pump, either by structural or functional abnormality of the organ. It can manifest in an acute, subacute or chronic form. In the acute form, symptoms appear suddenly, usually requiring hospital care for diagnosis and initial treatment. In chronic heart failure (HF), symptoms appear gradually, sometimes quietly at the beginning. (LOYAGA-RENDON RY, et al., 2015).

The most used classification is based on the left ventricular ejection fraction and/or through the severity of symptoms. There are three possibilities: normal left ventricular ejection fraction (≥ 50%), intermediate left ventricular ejection fraction (40-49%) and reduced left ventricular ejection fraction (<40%). This classification is very relevant because of the prognosis and response to clinical treatment (FELDMAN T, et al., 2018; ROHDE LEP, et al., 2018).

The pathophysiology of heart failure (HF) is centered on ventricular dysfunction. In normal cardiac physiology, cardiac output is maintained mainly by heart rate and stroke volume. In HF there is ventricular dysfunction, in the left ventricle it can be systolic or diastolic, depending on left ventricular ejection fraction (LVEF), <40% and> 40%, respectively, and its main consequence is the reduction of the output and the systemic tissue perfusion. In addition, it can be accompanied by an increase in stroke volume and final diastolic volume, which results in increased pressure in the left ventricle, which in turn
affects the atrium and pulmonary capillaries with elevations in pressure. There are many possible etiologies, some affecting systolic rather than diastolic function, others leading to impairment in both functions (KEMP CD and CONTE JV, 2012).

There may also be dysfunction of the right ventricle, usually as a consequence of dysfunction of the left. The dysfunctions may be related to a heart disease (cardiomyopathies) or be the result of changes in cardiac function due to chronic diseases. The etiology of heart failure (HF) differs according to the population analyzed, with ischemia being the most prevalent. Other etiologies are: hypertensive, chagasic disease, congenital cardiomyopathies, cardiotoxicity, alcoholic extracardiac diseases, tachycardiomyopathy, myocarditis and peripartum (KEMP CD and CONTE JV, 2012; ROHDE LEP, et al., 2018).

It is estimated that heart failure (HF) affected more than 23 million people worldwide in 2016 and this prevalence has grown, mainly due to the evolution of diagnostic methods and the increase in the population's average life span (ROHDE LEP, et al., 2018).

The therapeutic approach includes: pharmacological treatment, cardiac resynchronization therapy, implantable cardioverter defibrillator, surgical treatment, heart transplantation and mechanical circulatory support devices, which is the focus of this article (ROHDE LEP, et al., 2018).

The occurrence of heart transplantation, the gold standard for heart failure (HF) refractory to optimal medical management, is growing slowly, but remains a restricted option. It is in this scenario that mechanical circulatory support (MCS) devices has gained prominence, presenting itself as a therapeutic option for these patients, either as destination therapy or as a bridge for transplantation: worldwide, the proportion of using left ventricular assist device (LVAD) as a bridge has increased from 20 % to approximately 50% and as target therapy increased 10 times (LUND LH, et al., 2017; ROGERS JG, et al., 2017).

This review will elucidate the main aspects related to the use of mechanical circulatory support (MCS) in patients with heart failure. The most recent clinical trials show that mechanical circulatory support (MCS) is an alternative treatment that has obtained good results, mainly because they are an alternative to the gap between the need for transplant and possible transplants to be performed. Despite this, it is still under-indicated, preventing numerous patients from benefiting from its use.
2 METHODOLOGY

This is a systematic review which was researched on April 21, 2020 (Figure 1). Articles were selected from the Pubmed and Embase databases published between the years 2015 and 2020, of the type randomized controlled trial or not. The descriptors used were: assisted circulation AND artificial heart AND heart failure, and the descriptor artificial heart was not used for research at EMBASE. The search resulted in 2 articles in EMBASE searching through title, abstract, keywords, and the chosen keywords were: 'assisted circulation': ti, ab, kw AND 'heart failure': ti, ab, kw AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [2015-2020]/py, both articles included. And 40 at PubMed with the filters: Controlled Clinical Trial, published in the last 5 years, Humans. Of these 40 articles, 20 were excluded due to disagreement with the topic (2 of them because they were the same study at different stages, and 1 was excluded, but the most current was added instead in the search for similar articles).

Inclusion criteria were: randomized clinical trial study design or not, which addressed the theme of heart failure, circulatory support devices and artificial heart, in adults and elderly, english language. For exclusion, the criteria were: a different design that did not address the theme or the age of the participants. There were a total of 22 articles.

In this review, PICO (acronym for P: population / patients; I: intervention; C: control group; O: Outcome) was used as a strategy, as shown in (Table 1) and seeks to elucidate the main aspects related to the use of mechanical circulatory support in patients with heart failure.

<table>
<thead>
<tr>
<th>Population</th>
<th>Heart failure patients</th>
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<tbody>
<tr>
<td>Intervention</td>
<td>Use of mechanical circulatory support and total artificial heart in patients with heart failure</td>
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<tr>
<td>Comparison</td>
<td>Heart failure patients using other therapies</td>
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<tr>
<td>Outcome</td>
<td>Increased survival or quality of life</td>
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</table>

Source: De Paula LMM, et al., 2020
To analyze the methodological quality in this review, we chose to use the Cochrane Collaboration Tool to assess the risk of bias in clinical trials (DE CARVALHO A, et al., 2013).

The parameters used and presented in Table 2 were:

**Selection bias**, taking into account the Generation of random sequences, verifies if the groups produced are comparable, and if there was concealment of allocation, determines whether in the initial recruitment process it was possible to predict which group would receive which intervention;

**Performance bias**, takes into account the presence or absence of blindness on the part of professionals and research participants;

**Detection bias**, evaluates the possibility of prediction of outcomes by the evaluators;

**Attrition bias**, takes into account data losses and their relationship with outcome of interest;
Reporting bias, evaluates the possibility of published outcomes having been selected; 

Other sources of bias, which incorporates analysis of the study design option consistency, confusion bias, tools available for assessing outcomes or other circumstantial interferences.

<table>
<thead>
<tr>
<th>Mention</th>
<th>Selection bias</th>
<th>Performance bias</th>
<th>Detection bias</th>
<th>Friction bias</th>
<th>Reporting bias</th>
<th>Other biases</th>
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<td>HEATLEY G et al., 2016</td>
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<td>JUNG M.G. et al., 2015</td>
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3 RESULTS

Among the selected articles, most fit in one of these large studies: MOMENTUM 3, REDUCE-LAP, DECIDE-LVAD as described in Frame 1. MOMENTUM 3 was a randomized clinical trial without masking, which compared the use of the Left Ventricular Assist Device HeartmateIII with the Left Ventricular Assist Device HeartmateII in patients with advanced and refractory heart failure, regarding the primary outcomes of disabling stroke free survival and the need for reoperation to change or remove the device. Analyzes were performed at 6 and 24 months after implantation of the device. A secondary analysis was carried out to assess the primary outcome of adverse events of hemocompatibility, and another secondary analysis aimed to evaluate cases of occlusion and obstruction to the outflow of the device by torsion, demonstrating that this occurrence was an adverse effect of low incidence but that demanded constant universal surveillance status for patients with left ventricular assist device heartmate III. The HeartmateII was superior to HeartmateIII in terms of primary outcomes (stroke and reoperation) and secondary outcomes (only thrombosis in the flow pump). There was no statistical difference regarding quality of life and functional class (MEHRA MR, et al., 2018; MEHRA MR, et al., 2019; GOLDSTEIN DJ, et al., 2017; URIEL N, et al., 2017; COWGER JA, et al., 2018, HEATLEY G, et al., 2016).

In this comparison scenario between devices there’s another multicentric randomized clinical trial that evaluated differences between the HeartmateII (axial continuous flow, technology used at the time) in the control group, and the Left Ventricular Assist Device HeartWare system (centrifugal continuous flow) in the test group, and its impacts on outcomes in 24 months (ROGERS JG, et al., 2017). Regarding survival free from disabling blows and the need to replace the device, there was no inferiority of the centrifugal flow pump.

There’s also a prospective, multicenter, non-randomized, controlled study of 200 patients with advanced heart failure Class III (NYHA IIIB) or class IV with outpatient symptoms that assessed the impact of using a HeartmateII device in patients with drug treatment, without use of intravenous inotropic (which despite being useful in improving the hemodynamic profile in advanced heart failure, their chronic use leads to survival rates of 10% to 20% in one year). The ROADMAP study compared patients with optimal medical management, who used intravenous inotropic, with patients who received an HeartmateII (ROGERS JG, et al., 2015). At the end of the study, it was found that the use of the device
increased survival, however there was a worsening of the INTERMACS classification profile and quality of life. Thus, it’s necessary to individualize the therapy of choice.

DECIDE-LVAD was a randomized, multicenter, unmasked clinical trial that evaluated the effectiveness of using auxiliary materials (videos, pamphlets and classroom course) rigorously developed by the study team, and relatively impartial in the educational process, in association with the existing material, as support in the shared decision-making process of implantation of Left Ventricular Assist Device as destination therapy in patients with end-stage heart failure (ALLEN LA, et al., 2018; WARRAICH HJ, et al., 2019; MCILVENNAN CK, et al., 2018). Education regarding the device is very relevant, although it does not reflect on the post-placement satisfaction of the device. The perception of the procedure is also related to the characteristics of the institution and the patient himself.

Other studies, outside of DECIDE-LVAD, address support measures for decision making and regret after implementing the device, one of which is patient-centered and the other, through video intervention and its impact on early care planning for patients with advanced heart failure. (KOSTIK KM, et al., 2016; E-JAWAHR A, et al., 2019). Another study demonstrated the importance of a discussion with care planning for patients who received left ventricular assist device compared to a group that received only usual medical care (METZGER M, et al., 2018).

In three articles found, one of the studies addressed was the REDUCE LAP-HF: a randomized clinical trial, multicentre, triple blind that evaluated patients with symptomatic chronic heart failure, with elevated left atrial pressure, who received the interatrial bypass device. The study compared the test group, which received the interatrial bypass device, and the control group, which performed an intracardiac echocardiogram without interatrial bypass device. (SHAH SJ, et al., 2018; FELDMAN T, et al., 2018; FELDMAN T, et al., 2016). There was a reduction in pulmonary capillary wedge pressure in 1 month, with a low risk of adverse cardiac, cerebrovascular or renal events. It isn’t known whether these are persistent effects.

Double-blind randomized clinical trial, Yau TM, et al. (2019); characterized mainly as low risk of bias, addresses the use of mesenchymal precursor cells as complementary therapy in patients with advanced heart failure using left ventricular assist device, to promote cardiac recovery. He compares the test group that performed intramyocardial injections of 150 million allogeneic mesenchymal precursor cells with the control group,
which had simulated treatment with cryoprotectant medium, however there were no statistically significant differences.

One article deals with the use of a device that allows obtaining pulmonary pressure data to assist in drug treatment, in the indication of advanced therapies, in addition to the management of the post-implantation device of left ventricular assist device (FELDMAN DS, et al., 2017). Another assesses whether there is an impact on the duration of the disease, before the implantation of mechanical circulatory support devices, on the responses to therapy. (LOYAGA-RENDON RY, et al., 2015). It was identified that patients with acute presentations of heart failure have a better prognosis with Left Ventricular Assist Device despite the clinical condition at the moment.

The assessment of pulmonary capillary wedge pressure was also used prospectively and evaluated, by means of echocardiography, the relationship between left ventricle end-diastolic volume and left ventricular filling pressure as a function of the rotation speed of the ventricular flow assist devices continuous. Simultaneous measurements of left ventricular pulmonary capillary wedge pressure and end-diastolic volume were performed during exercise testing with a ramp protocol. (JUNG MG, et al, 2015). It was concluded that the left ventricular diastolic diameter isn’t a good parameter to assess pulmonary capillary wedge pressure, that is, there are other factors that can determine the relationship between pump speed and left ventricular volume. In view of these results, we’re left with an assessment of the quality of the evidence available to seek its incorporation into a conscious practice.

<table>
<thead>
<tr>
<th>Mention</th>
<th>N</th>
<th>Methodological design</th>
<th>Comparison groups</th>
<th>Characterization of the intervention protocol</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHAH SJ, et al., 2018 (3)</td>
<td>44</td>
<td>RCT Triple masking</td>
<td>Inter-Atrial Shunt Device group vs control group</td>
<td>This RCT double-blind, multicenter, phase 2 of implantation of the Inter-Atrial Shunt Device versus a simulated procedure (femoral venous access and image of the interatrial septum without Inter-Atrial Shunt Device, 1 to 1, was performed in 22 centers in United States, Europe, and Australia in patients with New York Heart Association (NYHA) outpatient class III or IV heart failure,</td>
<td>After 1 year, shunts were patent in all patients treated with Inter-Atrial Shunt Device; MACCRE showed no significant difference in the Inter-Atrial Shunt Device group (2 out of 21 [9.5%]) compared to the control group (5 out of 22 [22.7%]; p = 0.4. In 1 year, the rate of hospitalizations for heart failure was 0.22 in the Inter-Atrial Shunt Device group and 0.63 in the control arm (P = 0.06).</td>
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<tr>
<td>YAU TM, et al., 2019</td>
<td>159</td>
<td>RCT Intramyocardial injection group of MPCs x</td>
<td>Randomized clinical phase 2 study involving patients with advanced heart failure, in which left ventricular assist device was implanted, in 19 North American centers (July 2015 to August 2017). The 1-year follow-up ended in</td>
<td>The average success rate of temporary weaning from left ventricular assist device support for more than 6 months was 61% in the MPC group and 58% in the control group (rate ratio [RR], 1.08; 95% CI, 0.83-1.31; P = 0.55). No patient had a primary safety outcome. Of the 10 pre-specified secondary outcomes reported, 9 did not reach statistical significance.</td>
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<tr>
<td>Study</td>
<td>N</td>
<td>Design</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Main Results</td>
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<td>ROGERS JG, et al., 2017</td>
<td>446</td>
<td>RCT</td>
<td>Centrifugal flow device (test group) x Axial flow device (control group)</td>
<td>A randomized multicentre study was carried out involving 446 patients who were assigned, in the proportion of 2:1, to the study device (centrifugal flow) or to the control device (axial flow).</td>
<td>Left ventricular assist device was implanted in patients with advanced heart failure who could not undergo a transplant. Intrapericardial centrifugal flow left ventricular assist device was not inferior to atrial flow left ventricular assist device when we analyzed stroke-free survival or the need to remove the device due to malfunction. Quality of life and functional capacity showed similar improvement in both groups.</td>
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<td>MEHRA MR, et al., 2018 (1)</td>
<td>366</td>
<td>RCT Open Label</td>
<td>Patients using left ventricular assist devices: Centrifugal continuous flow pump x Axial continuous flow pump</td>
<td>In a randomized study to assess non-inferiority and superiority, centrifugal flow pumps were compared with the axial flow pumps in patients with advanced heart failure, regardless of whether they were for transplantation or destination therapy. The primary outcome measure was to assess survival after 2 years free of disabling stroke (with disabling stroke indicated by a modified Rankin score ≥ 3; scores range from 0 to 6, with higher scores indicating more severe disability) or survival free of reoperation to replace or remove malfunctioning device.</td>
<td>Of the 366 patients, 190 were assigned to the centrifugal flow pump group and 176 to the axial flow pump group. In an analysis of the intention-to-treat population, the primary outcome occurred in 151 patients (79.5%) in the centrifugal flow pump group, compared with 106 (60.2%) in the axial flow pump group (absolute difference, 19.2%; points; 95% lower confidence limit, 9.8 percentage points [p &lt;0.001 for non-inferiority]; risk rate 0.46; 95% confidence interval [CI], 0.31 to 0.69 [P &lt;0.001 for superiority]). Reoperation due to pump malfunction was less frequent in the centrifugal flow pump group than in the axial flow pump group (3 patients [1.6%] vs. 30 patients [17.0%]; risk rate 0.08; 95% CI, 0.03 to 0.27; P &lt;0.001). The rates of death and disabling stroke were similar in the two groups, but the overall rate of stroke was lower in the centrifugal flow pump group than in the axial flow pump group (10.1% vs. 19.2%; risk rate of 0.47; 95% CI, 0.27 to 0.84, P = 0.02). In patients with advanced heart failure, a magnetically levitated centrifugal flow pump was superior to a mechanical bearing axial flow pump in relation to disabling stroke-free survival or reoperation to replace or remove a defective device.</td>
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<tr>
<td>MEHRA MR, et al., 2019 (1)</td>
<td>102</td>
<td>RCT Open Label</td>
<td>Patients using left ventricular assist devices: Centrifugal continuous flow pump x Axial continuous flow pump</td>
<td>Patients with advanced heart failure were randomly assigned to receive a centrifugal or axial flow pump, regardless of the intended use objective (bridge for transplantation or destination therapy). The primary composite endpoint was 2-year stroke-free survival or disabling reoperation to replace or remove a defective device. The main secondary outcome was the pump replacement in 2 years.</td>
<td>This final analysis included 1028 enrolled patients: 516 in the centrifugal flow pump group and 512 in the axial flow pump group. In the final analysis of the primary outcome, 397 patients (76.9%) in the centrifugal flow pump group, compared with 332 (64.8%) in the axial flow pump group, remained alive and without stroke or reoperation incapacitating to replace or remove a malfunctioning device in 2 years (relative risk, 0.84; 95% confidence interval [CI], 0.78 to 0.91; P &lt;0.001 for superiority). Pump replacement was less common in the centrifugal flow pump group compared to the axial flow pump group (12 patients [2.3%] vs. 57 patients [11.3%]; relative risk, 0.21; 95% CI, 0.11 to 0.38; P &lt;0.001). The number of events per patient-year for stroke of any severity, severe bleeding and gastrointestinal bleeding was lower in the centrifugal flow pump group than the axial flow pump group.</td>
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</table>
| FELDMAN N, N, et al., 2018 | 44 | RCT Triple masking | Inter-Atrial Shunt Device group x control group | REDUCE LAP-HF I (Reduce Elevated Left Atrial Pressure in Patients With Heart Failure) was a multicenter, blinded, phase 2, randomized, parallel group study in patients with heart failure class III or outpatient class | In all, 94 patients were included, of which only 44 met the inclusion criteria, being randomized to the DDIA (n = 22) and control (n = 22) groups. The mean age was 70 ± 9 years and 50% were female. After 1 month, the DDIA group resulted in a greater reduction in Pulmonary capillary wedge
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| 182  | 5     | 2018 | Shared decision making for destination therapy with left ventricular assist device: modestly improved the quality of the patient's decision, as measured by knowledge and agreement between declared values and the choice of treatment reported by the patient. However, there was no improvement in the agreement between the declared values and the actual treatment received. The rate of left ventricular assist device implantation was substantially lower in the intervention compared to the control group. | FEL DMA N DS, et al., 2018 | It was possible to observe a lower tendency (but without a statistically significant difference) in the time to implement advanced techniques for the treatment of heart failure in the group that underwent intervention (168.6 ± 131.8 versus 265.7 ± 210.3 days; RR: 1.72; 95% CI 80–370; p = 0.13). There was also a difference in the number of medication changes, with the control group undergoing fewer changes (10.8 ± 6.0 vs. 8.3 ± 8.4; p = 0.14), however the difference was not statistically significant. The time interval between implantation of left ventricular assist device until the need for transplantation or termination of study was lower in patients in the intervention group ((202.0 ± 162.8 x 284.8 ± 153.8 days); RR, 9.53; 95% CI, 2.34 – 38.73; p < 0.01). The proportion of bridged patients for transplantation was higher in the intervention group (7 patients in the group that underwent intervention against 1 patient in the control group, p = 0.045). | Group that received clinical guidance \( x \) Group that did not receive guidance |}

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| 239  | 2     | 2019 | Of the 239 patients, left ventricular assist device recipients \( (n = 164) \) and non-left ventricular assist device recipients \( (n = 75) \) had a similar proportion with ≥1 comorbidity (70% vs. 80%, \( P = 0.09 \)). Patients with comorbidities were younger, regardless of the status of implantation of left ventricular assist device. After adjusting for age, in the total group of patients and among left ventricular assist device recipients, patients with ≥1 comorbidity had a higher mean decision conflict at the beginning (23.2 ± 1.5 vs. 17.4 ± 2.2) and, at 6 months, greater stress (13.0 ± 0.6 vs. 10.4 ± 1.0), and fight against the disease (13.3 ± 0.6 vs. 11.1 ± 0.6) than those without comorbidities \( (P <0.05) \). No difference was observed in the decision regret, PHQ-2, EQ-VAS, disease acceptance and overall survival and between left ventricular assist device recipients. | WAR RAIC H HJ, et al., 2019 | Individuals were included in DECIDE-LVAD, a multicenter study, patients considering left ventricular assist device, so that their comorbidities were registered using the INTERMACS protocol. We compared decision conflict, regret, perception of stress, quality of life (EQ-VAS), depression (PHQ-2), struggle with and/or acceptance of the disease due to the weight of comorbidities among the most common comorbidities. | Patients with left ventricular assist device \( x \) Patients without left ventricular assist device |}

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<tr>
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| 182  | 5     | 2018 | At the beginning of the study and during the follow-up, decision regret, perceived stress, preparation for care, depression and satisfaction with care were not significantly different between the control and intervention groups. In one month, after excluding the undecided, ineligible and pending medical evaluation, the stated treatment preferences were approximately the same in both groups: “the loved one wanted destination therapy- left ventricular assist device and decided to obtain it” and “the loved one decided first not receiving left ventricular assist device, but later decided he wanted to” (control group, 96.4%, intervention group, 89.2%; \( p = 0.12 \)). The agreement between the caregiver's | MCI LVE RNA N CK, et al., 2018 | All sites began the control period using only their existing decision, educational and consent materials during formal education (sector pamphlets and videos and specific documents on left ventricular assist device). At four-step time intervals, programs were randomly assigned to transition to intervention. | Caregivers of patients considering left ventricular assist device who received guidance \( x \) Caregivers of patients |}

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| (3)  |       |      | IV of the Cardiac Association of Nova York, EF ≥40%, Pulmonary capillary wedge pressure ≥25 mm Hg during exercise and Pulmonary capillary wedge pressure-right atrial pressure gradient ≥5 mm Hg. Randomization (1:1) separated the participants for the Inter-Atrial Shunt Device or for a simulated procedure (femoral venous access with intracardiac echocardiography, but without placement of the Inter-Atrial Shunt Device. | ALL EN LA, et al., 2018 | From 2015 to 2017, a randomized study, with staggered levels, was carried out at 6 left ventricular assist device implantation centers in the USA, including 248 patients undergoing treatment for destination therapy with left ventricular assist device. | Group that received clinical guidance \( x \) Group that did not receive guidance |}

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Study Design</th>
<th>Study Type</th>
<th>Participants</th>
<th>Primary Objective</th>
<th>Clinical Trials</th>
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<tbody>
<tr>
<td>FELDMA NT, et al., 2016 (3)</td>
<td>60</td>
<td>RCT Triple masking</td>
<td>Patients with transeptal puncture and Inter-Atrial Shunt Device system II guided by fluoroscopy and intracardiac echocardiogram by X intracardiac echocardiogram by with examination of the atrial septum and assessment of the left atrium</td>
<td>The primary objective was the analysis of peri-procedural safety and the potential effectiveness (mechanical effect) of the implantation of the Inter-Atrial Shunt Device system in patients with heart failure with left ventricular ejection fraction &gt; 40% and high filling pressure of the left heart who remained symptomatic despite of targeted pharmacological therapy already optimized by the guideline.</td>
<td>The clinical trial supports the safety of the implantation procedure, the safety of the device itself after implantation and the hemodynamic and clinical improvements. The new study currently described will be the first prospective, multicenter, randomized, blind study to test this strategy and has strong potential to provide important data to deepen the knowledge of this innovative therapy, based on transcatheter devices for heart failure with preserved ejection fraction.</td>
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<tr>
<td>MEHRA MR, et al., 2018 (1)</td>
<td>366</td>
<td>RCT Open Label</td>
<td>Centrifugal HeartMate III x Axial HeartMate II</td>
<td>In 366 patients randomly assigned, 361 were selected for treatment (189 in the HeartmateII group and 172 in the HeartmateII group), 337 (177 in the HeartmateIII group and 160 in the HeartmateII group) being discharged after implantation. The HeartmateII arm had a lower number of total hospitalizations per patient-year (HeartmateII: 2.1 ± 0.2 versus HeartmateII: 2.7 ± 0.2; P = 0.015) and 8.3 fewer hospital days per patient-year on average (HeartmateIII: 17.1 days versus HeartmateII: 25.5 days; P = 0.003).</td>
<td>In this two-year economic analysis of the MOMENTUM 3 study, HeartmateIII demonstrated a reduction in readmissions, hospital days during readmissions and significant cost savings after discharge, compared to the HeartmateII left ventricular assistance system, regardless of the intended objective of therapy.</td>
</tr>
<tr>
<td>GOLDST DJ, et al., 2018 (1)</td>
<td>289</td>
<td>RCT Open Label</td>
<td>Heartmate III Patients x Heartmate II Patients</td>
<td>Cox’s proportional risk models were used to analyze patients enrolled in the “treated group cohort” (n = 289) of the MOMENTUM 3 study to: (1) determine the interaction of several subgroups in the main end results; and (2) to identify independent variables associated with the success of the primary outcome.</td>
<td>Baseline characteristics were well distributed between the HeartmateIII (n = 151) and HeartmateII (n = 138) cohorts and it was not possible to observe a significant difference between the subgroups with regard to primary outcomes. Cox's multivariable modeling identified age (≤65 years vs&gt; 65 years, risk rate 0.42 [95% confidence interval 0.22 to 0.78], p = 0.006) and type of pump (HeartmateIII vs HeartmateII, risk rate 0.53 [95% confidence interval 0.30 to 0.96], p = 0.034) as independent predictors of success in primary outcomes. After adjusting for age, there was no significant impact of gender, race, therapeutic intent and INTERMACS profiles on primary outcomes.</td>
</tr>
<tr>
<td>UREILN, et al., 2017 (1)</td>
<td>289</td>
<td>RCT Open Label</td>
<td>Heartmate III Patients x Heartmate II Patients</td>
<td>The intervention was carried out by the MOMENTUM 3 study, with the implantation of ventricular assist devices (“pump”) type HeartmateII and HeartmateIII</td>
<td>Survival free of clinically important hemocompatibility events at 6 months was significantly higher in HeartmateIII than in HeartmateII (69 ± 4% versus 55 ± 4%; risk rate of 0.62; 95% CI, 0.42-0.91; P = 0.012). They also performed this analysis stratifying age, as previous studies have shown that age greater than or equal to 65 years the risk of these events increases substantially. Age ≤65 years: the HeartmateIII group showed a greater absolute difference compared to HeartmateII (76 ± 5% versus 58 ± 5%; risk rate 0.51; 95% CI, 0.30-0.87; P = 0.01). Age &gt; 65 years, the results remained numerically better for the HeartmateIII group, although P values &gt; 0.05. The patients with...</td>
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</table>
A great process thinking about the user was carried out, with a randomized study of Decision Aid (DA) compared to standard education among hospitalized patients considering treatment with left ventricular assist device for advanced heart failure. The main outcomes were the knowledge of left ventricular assist device in 1 week and after 1 month having been administered the DA versus standard education, using a previously validated scale. Secondary measures included pre-specified quality decision-making measures recommended by the International Patient Decision Aid Standards Collaboration.
ventricular assist device was used and the presence or absence of serious adverse events.

At the checkpoints described above, the number of patients with criteria for good response to the use of left ventricular assist device was also assessed (NYHA I / IL, 6-minute walk test with gait greater than 300m and satisfactory quality of life as to the study variable (criterion: general KCCQ > 50).

Similarly, there was an equivalent improvement in distance from 6MWT at 6 months in HeartmateIII (+94 [1-274] meters) and in HeartmateIII (+188 [43-340] meters) compared to measurements at baseline.

In patients with severe adverse effects (n = 188), the walking tests increased (p <0.001), however the increase was lower when compared to the group without serious adverse events (HeartmateIII: +74 [-9 to 183] meters with events vs +140 [35-329] meters without events; HeartmateII: + 177 [47-356] meters with events vs +192 [23-337] meters without events, both p <0.003).

Serious adverse events did not affect the quality of life indexes and it was found that 145 HeartmateIII patients (63%) and 120 HeartmateII (68%) met the criteria for good response to left ventricular assist device (p = 0.44).

### Table 1: Study Design and Participants

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Study Design</th>
<th>Treatment</th>
<th>Participants</th>
<th>Primary Outcome Measures</th>
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</table>
| LOY AGA - REN DON RY, et al., 2015 | RCT         | Acute heart failure x subacute heart failure x chronic heart failure, all with mechanically assisted circulatory support (MCS) | Patients who received left ventricular assist device were stratified using INTERMACS and duration of their symptoms: acute heart failure, ≤1 month; subacute heart failure, 1-12 months) and chronic heart failure, ≥12 months and followed up receiving heart failure support for the duration of the study. | At the evaluation, INTERMACS 1, 60%, 24% and 13.2% were from the acute heart failure, subacute heart failure and chronic heart failure groups, respectively (p = 0.0001). Greater use of biventricular support was on the part of patients with chronic heart failure (14.4%) and 29% of patients in that same group received transplants vs 22.6% of those with chronic heart failure. The 4-year survival rate (estimated) was 58%, 51% and 45% for patients with acute heart failure, subacute heart failure and chronic heart failure (p = 0.006).

And after adjusting for known risk factors for adverse outcome, patients with acute evolution have a better prognosis in late stages (risk rate of 0.34; P = 0.0003). It was concluded that the duration of the symptoms of heart failure is an important prognostic factor for the use of left ventricular assist device. |
| EL-JAWAH A et al., 2016 | RCT Open Label | Verbal clarifications + informative video + advanced care planning (ACP) checklists vs only verbal description / clarifications | The intervention consisted of a verbal description of the options of treatment goals in the final care of life, defining approaches such as prolonging life or comfort, when addressing topics such as CPR / intubation. An explanatory 6-minute video was also exposed and a checklist of the advanced care planning was applied. Control patients only received a verbal description. | In the intervention group 27 (22%) vs 50 (41%) chose long-term care, 31 (25%) vs 27 (22%) chose limited care, 63 (51%) vs 37 (30%) selected a focus on comfort and only 2 (2%) vs 8 (7%) were not sure of the option. (P <0.001).

More frequently, patients in the intervention group renounced CPR (68% versus 35%; P <0.001) and intubation (77% versus 48%; P <0.001), in addition, demonstrated a higher level of knowledge (score 4.1 versus 3, 0; P <0.001). |
| METZGE R M, et al., 2016 | RCT patient masking | SPIRIT-HF + usual care vs usual care only | RCT in which patient-caregivers were randomized with equal allocation (1: 1) between the comparison groups. The SPIRIT-HF intervention consisted of a structured and guided discussion, carried out by a properly trained interventionist, in a single session lasting approximately one hour. The intervention addressed understanding of the disease and the meaning of the use of devices, gaps and concerns, as well as alignment of goals, planning and synthesis. | 29 patient-caregivers (76% of the initial ones) were enrolled. randomized and completed the study.

The intervention group characterized the protocol as beneficial. All patient-caregiver sets showed improvement in results, with no statistically significant difference. However, the intervention group tended to align more closely with the end of life directive points. |
<p>| HEATLE - | RCT project | HeartmateIII x HeartmateII | The study aims to verify the effectiveness, safety and non-inferiority of HeartmateIII in | In this sense, it is important to highlight that the study was designed for patients with advanced heart failure, regardless |</p>
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Study Design</th>
<th>Methodology</th>
<th>Outcome Measures</th>
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<tr>
<td>Y G. et al., 2016</td>
<td>10</td>
<td>Echocardiography</td>
<td>Patients with continuous-flow left ventricular assist device vs. what has been established for patients without mechanical support. The parameters found were also compared between two evaluators.</td>
<td>Using a ramp test, the evaluation was divided into two basic stages of the ramp and then a low ramp, the pulmonary capillary wedge pressure was simultaneously measured by the Swan-Ganz catheter and the diameter of the left ventricle in the final diastolic phase by echocardiography, seeking to verify the pressure-volume ratio as a function of the pump RPM of the device used. When climbing the slope of the ramp, 400 RPM / 5 minutes was increased until reaching 12,000 RPM or suction / arrhythmic event (high ramp). Finally, the test was completed with a 25-watt exercise test.</td>
</tr>
<tr>
<td>JUN G MG. et al., 2015</td>
<td>200</td>
<td>HeartMate II x optimized medical treatment, both NYHA IIIB / IV</td>
<td>The ROADMAP study is a prospective, multicenter, non-randomized study of 200 NYHA IIIB / IV patients who were undergoing outpatient follow-up. They were separated into two groups, maintained on optimized drug treatment or given a device, HeartmateII. The study consisted of a 2-year follow-up in order to verify the survival of patients with improvement in the 6-minute walk, for a distance = 75m. Secondary outcomes were also evaluated, such as heart attacks, bleeding, need for reoperation, quality of life, degree of symptomatology and application of a questionnaire about the patient's desire in a decision-making situation.</td>
<td>At the base of the ramp, the pump rotation had $9,300 \pm 241$ RPM (in which 3 out of 10 had aortic valve opening). In the low ramp, base ramp and high ramp, the pulmonary capillary wedge pressure were $20 \pm 4$, $14 \pm 4$ and $7 \pm 3$ mmHg ($p &lt; 0.001$ for all comparisons) and ventricular diameter $6.6 \pm 1.0, 6.7 \pm 0.9$ and $5.5 \pm 1.7$ cm ($p &lt; 0.05$ for all comparisons, except low ramp versus ramp base). From the analysis of the correlation between ramp slope, pulmonary capillary wedge pressure and ventricular diameter, it is concluded that pulmonary capillary wedge pressure as a function of RPM is weakly correlated with changes in ventricular diameter and, therefore, the measurement of the diameter is not an accurate measure of discharge in patients in use of the left ventricular assist device with continuous flow, there are other factors that influence the relationship between the pump's operating speed and the left ventricle volume.</td>
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Subtitle: MOMENTUM 3 (1), DECIDE-LVAD (2), REDUCE LAP-HF (3), article found in the search for similar (4)


Three articles did not make explicit whether there was data loss with their justifications, and only KOSTIK KM, et al. (2018); and METZGER M, et al. (2016) presented significant data loss due to the discontinuity of the follow-up by some participants. Only in 3 articles it was not possible to establish whether there was selective reporting and only in METZGER M, et al. (2016) was it identified as a high risk of reporting bias.
In 9 studies, a high risk of other bias was identified, among which we highlight sponsorship and other technical limitations, such as the MOMENTUM 3 study, which received sponsorship from the company responsible for HeartmateIII and HeartmateII and was directly interested in proving its non-existence, inferiority and superiority, representing 7 of the 9 studies commented.

In METZGER M, et al. (2016); structured questions related to limitations of the intervention site and semi-structured interview with consequent variation and with its strong subjectivity character may have worked as confusion biases.

In the case of ROGERS JG, et al. (2017); changes in the research protocol that may have worked as confusion biases, stand out the individualization of the anticoagulation protocol and structural change of the device during the research that may have influenced the outcomes studied, such as strokes.

In DECIDE-LVAD, although no blinding aspects of the study were mentioned and how the allocation of participating caregivers was carried out, it used measures of knowledge scores, values and items to be scored, that is, objective criteria for analyzing the outcomes. It was conducted in several centers, allowing data collection on the characteristics of caregivers. Thus, it can be considered as a high risk of bias in terms of selection, performance and detection bias.

In REDUCE LAP-HF, since it was a randomized clinical trial, double-blind, multicentric, in terms of detection bias, although the blindness of the evaluators was not commented, it is believed that the results of the study would not be harmed by this fact.

Studies for suggesting educational protocols regarding procedures such as METZGER M, et al. (2016); and KOSTIK KM, et al. (2018); showed greater difficulty in adherence by patients, which results in recurrent patient losses due to withdrawal from research protocols, potential generators of bias recognized by the authors. It is noteworthy that, despite the training of the professionals responsible for executing the protocol and other measures that aim to soften the interference, the user profile of a specific system, level of prior instruction related to the object of study, as well as the intention to offer the best treatment works as potential biases, mainly in data collection.

It is clear that the studies included in the present review show efforts in the search for the best quality of available evidence, however they must be critically interpreted, taking into account its limitations here exposed, for application in good clinical practice.
4 DISCUSSION

The mechanical circulatory support consists of a set of devices responsible for providing hemodynamic assistance to patients who have failed heart physiological pumping, those with advanced heart failure (DESAI SR and HWANG NC, 2018). Ventricular assist devices offer mechanical circulatory support to patients with heart failure refractory to optimal medical management and can be directed to the left ventricle, right or biventricular. Ventricular assist devices can be implanted percutaneously, minimally invasive surgery or thoracotomy, offering pulsatile, continuous axial or centrifugal blood flows. Although it’s primary function is to replace the cardiac pumping function, left ventricular assist device also reduces it’s remodeling process, and improves myocardial function in a minority of patients (YAU TM, et al., 2019).

The HeartmateII is a surgically implanted left ventricular assist device, capable of offering long-term mechanical circulatory support. It’s a second generation device that offers continuous axial blood flow, through a pump that functions as a helix inserted into a cannula, connecting the left ventricle to the ascending aorta, with the rotating element suspended by mechanical bearings. It features a portable battery lasting 6 to 8 hours on a single charge. (DESAI SR and HWANG NC, 2018). The HeartmateIII is also a left ventricular assist device that works as an intrathoracic pump coupled to the left ventricular, and can be used in an intra or extra-hospital environment. It’s a long-term, third generation device that offers a continuous centrifugal flow, maintaining an impeller rotating levitated without contact or mechanical bearings, through a magnetic field. This impeller is coupled to the left ventricle, promoting a force that impels the blood through a cannula that connects to the ascending aorta. The HeartmateIII has the capacity to pump blood up to 10 L/min and its speed is in the range of 3,000 to 9,000 rpm (MEHRA MR, et al., 2019). The pump has an optimized fluid dynamics, with a large blood flow, designed to prevent stasis and, consequently, the formation of thrombi, since it was planned exclusively to improve the hemocompatibility of the blood device interface (URIEL N, et al., 2017). HeartWare is a third generation ventricular assist device that features continuous centrifugal flow, magnetic levitation and hydrodynamics of the internal rotor. It’s implanted in the pericardial space, with an entry cannula integrated with the left ventricle (ROGERS JG, et al., 2017).

The use of mesenchymal precursor cells has been proposed as adjunctive therapy to left ventricular assist device, with the potential to cause a greater degree of myocardial recovery and improvements in left ventricle function. Mesenchymal precursor cells have a
local immunosuppressive quality, reducing myocardial inflammatory response, preventing infections, bleeding and thrombosis (YAU TM, et al., 2019).

The implantable hemodynamic monitoring system was developed to assist in the optimization of heart failure therapy for certain patients and in the decision of the ideal moment for the implantation of left ventricular assist devices. The CardioMEMS heart failure device is implanted in the pulmonary artery and has a sensor to detect changes in blood pressure, which can mean worsening of the heart failure condition, even in asymptomatic patients. He sends this information to the doctor, who, by analyzing pressure variations in the pulmonary artery, can make changes to the patient's drug treatment or evaluate other possible therapies. The use of this device is related to reducing the risk of hospitalization of patients with heart failure with reduced left ventricular ejection fraction and preserved left ventricular ejection fraction (FELDMAN DS, et al., 2018).

Inter-atrial shunt device ® is indicated for heart failure with preserved or slightly reduced left ventricular ejection fraction, refractory to optimal medical management. The inter-atrial shunt device ® is placed in the interatrial septum, allowing an blood flow from the left atrium to the right atrium; thus there is a reduction in pressure in the left heart and pulmonary congestion. It’s radiopaque and echogenic, allowing imaging to be performed during implantation (SHAH SJ, et al., 2018; FELDMAN T, et al., 2018; FELDMAN T, et al., 2016).

Studies agree that HeartmateIII superior to HeartmateII, demonstrating a higher survival rate and a lower frequency of pump replacement in 2 years. HeartmateIII demonstrated a lower rate of adverse effects, including stroke, pump thrombotic events and bleeding. There was no significant difference in overall survival when we assessed HeartmateIII and HeartmateII, and the most frequent causes of death in patients were right heart failure, stroke and infection. In turn, studies have verified compatibility in the effectiveness of the devices, HeartmateII and HeartWare, in demonstrating 2-year stroke-free survival or need to replace the devices. The use of HeartWare was associated with more cerebral vascular events, sepsis and right heart failure, while the use of HeartmateII caused a higher rate of emergency transplantation, exchange or removal of the device. Concerning adjuvant therapies, the use of mesenchymal precursor cells is included, which demonstrated, due to the weaning rate of the device for more than 30 minutes, that they do not interfere in the response to the implantation of the left ventricular assist device, therefore, its use in patients with eligible heart failure left ventricular assist device is not indicated. The
implantation of a pressure sensor in the pulmonary artery was evaluated in the CHAMPION study, demonstrating that there is a benefit in its use to determine the best time for intervention in heart failure and treatment optimization. (GOLDSTEIN DJ, et al., 2017; URIEL N, et al., 2017; COWGER JA, et al., 2018; MEHRA MR, et al., 2018; YAU TM, et al., 2019; ROGERS JG, et al., 2017; LUND LH, et al., 2018; FELDMAN DS, et al., 2017).

According to the INTERMACS registry, patients with acute heart failure are mostly women, young, without history of cardiac surgery or peripheral vascular disease. Patients with acute heart failure tend to have a more severe INTERMACS profile, requiring emergency intervention, and sometimes biventricular mechanical circulatory supports. As for the need for heart transplantation, patients with acute heart failure have a slightly greater need than patients with chronic heart failure. The estimated 4-year survival and long-term prognosis in patients with chronic heart failure is worse when compared to acute heart failure (RENO YLR, et al., 2015).

The inter-atrial shunt device® was effective in reducing pulmonary capillary wedge pressure and the rate of hospitalization for heart failure in one year, but it was no more effective than the control group in the result of the 6-minute exercise test, not even in the quality of life. Comparing the inter-atrial shunt device® and the intracardiac echocardiogram, there was no difference regarding cerebrovascular, cardiac or renal events. There was a right ventricular increase 6 months after the implantation of inter-atrial shunt device®, however, this increase was not permanent after 12 months (SHAH SJ, et al., 2018; FELDMAN T, et al., 2018).

In this systematic review, there was no pair of reviewers to assess the eligibility and exclusion criteria of the selected literature, furthermore, there was no confrontation of information between reviewers.

5 FINAL CONSIDERATIONS

When, despite the optimal medical management, the cardiac pump remains in bankruptcy, invasive techniques such as transplantation and mechanical circulatory support become final resources, the first of which is hampered by the low availability and compatibility of donors. The analysis of the works listed here showed that left ventricular assist device are effective measures in the survival of patients with heart failure, and can be used both as a bridge for rehabilitation and transplantation or even destination therapy. Other interventions, such as the implantation of mesenchymal precursor cells and inter-atrial
shunt device®️, were not shown to be significantly effective. Therefore, this analysis suggests that mechanical circulatory support devices are constantly evolving and deserve special attention in the management of patients with severe heart failure. Advised to carry out further studies to improve the indication criteria, making it possible to allocate resources in hospitalized patients who benefit from this type of mechanical circulatory support service.
REFERENCES


