

Summary

Evaluation of the evidence on the HeartMate II® and HeartWare® ventricular assist devices for the treatment of chronic end-stage heart failure

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SUMMARY

Evaluation of the Evidence on the HeartMate II® and HeartWare® Ventricular Assist Devices for the Treatment of Chronic End-Stage Heart Failure

Context

Heart failure is a complex syndrome that arises when the heart is incapable of pumping enough blood to respond to the metabolic needs of the body. Heart failure is often caused by defective contraction and relaxation of the myocardium, accompanied by elevated cardiac filling pressure. It represents the final stage of a number of cardiovascular diseases. Characterized by limitation in activities of daily living and progressive exhaustion at rest, heart failure is a disabling and life-threatening condition. Severe heart failure, defined as class IV using the functional classification scheme of the New York Heart Association (NYHA), is associated with a 1-year mortality of about 50%.

Heart failure is a major public health problem, associated with high rates of morbidity and mortality. It is estimated that more than 80,000 people are affected in Quebec, and the incidence of heart failure is expected to increase as a result of ageing of the population. More than 75% of patients suffering from heart failure in Quebec use hospital-based services. Approximately 8,500 people are hospitalized each year; about 85% of these patients are 66 years or older. More than 900 people die from heart failure annually in Quebec.

End-stage chronic heart failure is characterized by advanced modifications of the cardiac system, marked symptoms at rest, and is refractory to medical and surgical treatment. Cardiac transplantation is the treatment of choice for most cases of end-stage chronic heart failure. However, access to cardiac transplantation remains relatively limited due to strict eligibility criteria and a lack of donor organs.

An implantable ventricular assist device (VAD) is a technology that has been offered in Canada since 1986 and for which demand continues to grow. A VAD increases cardiac output by reducing the work of the failing heart. It is thus used to improve the chances that a patient survives until receipt of a donor heart (or, occasionally, until recuperation of cardiac function) or for long-term treatment in the case of temporary or permanent ineligibility for heart transplantation. In the past decade, VAD technology has evolved, in order to reduce the number of moving parts and device size and to increase durability; thus, newer “continuous-flow” devices have taken the place of pulsatile-flow VADs.

In 2010, the Quebec Tertiary Cardiology Network (the Réseau québécois de cardiologie tertiaire, RQCT) produced a narrative review on VADs and an analysis of the situation in Quebec from 2000 to 2008. Currently, three hospitals in Quebec carry out cardiac transplantation and use implantable VADs for adult patients. In 2011, the Ministry of Health and Social Services (MSSS) gave the Institut national d'excellence en santé et en services sociaux (INESSS) the mandate to perform an evaluation of implantable VADs. Our analysis focusses on the two continuous-flow VADs that are the most relevant to the Quebec context: HeartMate II®, the device that is the most often used in Quebec, and HeartWare®, an emerging technology in Europe.

The objectives of this evaluation are to:

1. synthesize, by means of a systematic review, the recent evidence (2008-2011) on HeartMate II® (HM II) and HeartWare® (HW), with regard to effectiveness, safety and economic considerations, according to initial indication (bridge to transplantation or permanent “destination” therapy) for patients with end-stage chronic heart failure; and
2. provide an overview, by means of a narrative review, of organizational and ethical issues in VAD use, including the process of patient selection.

Methods

A systematic search of the scientific literature published between January 2008 and April 2011 was carried out in bibliographic databases. We performed a final update of the search in January 2012 in order to identify any new articles published on economic issues, end-organ function and on HW, since limited information was found on these aspects. We also looked for follow-up publications for studies identified during our initial search.

In order to summarize pertinent material on organizational aspects and eligibility of patients, we extracted information from the following sources: 1) the most recent clinical practice guidelines on management of heart failure from North America and Europe; 2) health technology assessment (HTA) reports published between 2008 and 2010; and 3) expert consensus documents found during our literature search. Document selection, extraction of data, and critical analysis of studies was carried out independently by two members of the INESSS team.

Data on the number of VADs implanted were obtained from the three transplantation centres in Quebec, from publications, and through communication with key contacts in other regions.

We created a scientific committee of expert clinicians, consisting of a cardiologist and cardiac surgeons representing each transplantation centre in Quebec and the RQCT. This committee played an advisory role with regards to validating our methods and assuring both the rigour of our evaluation and the appreciation of elements relevant to the clinical perspective in Quebec.

Results

In our systematic review of clinical outcomes, 13 studies on HM II met our selection criteria, with 8 examining VAD support in patients waiting for a heart transplant (719 “bridge to transplant” patients) and 5 examining VAD support as destination therapy (414 patients). Almost all the studies were carried out in USA. Two arose from INTERMACS (the Interagency Registry for Mechanically Assisted Circulatory Support). One international multicentre study was found on HW (50 “bridge to transplant” patients).

In the studies we analyzed, destination therapy patients were, on average, 10 years older than bridge-to-transplant patients; the average age of the latter was about 50 years. The mean duration of VAD support varied from 8 to 10 months for patients awaiting transplantation and from 19 to 21 months for destination therapy patients. According to the most recent INTERMACS report, eligibility for heart transplantation is uncertain for the largest proportion of patients receiving a VAD (about 40% of recipients in 2010). Also, patients originally receiving a VAD as destination therapy may eventually receive a heart transplant, and those receiving a VAD as a bridge to transplant may keep the device indefinitely. Some patients in both of these groups can experience enough improvement of cardiac function to be able to have their VAD removed (explanted). Thus, the various classes of VAD users can overlap.

According to our systematic review of effectiveness, safety and economic considerations:

1. The use of a continuous-flow implantable VAD (HM II or HW) can be considered a clinically-effective therapeutic option, compared to optimal medical treatment, if offered to appropriate patients. For both bridge to transplant and destination therapy patients, results are promising for survival, as well as for impact on function and on quality of life. Of 100 patients receiving a HM II device, more than 70 will be alive on support at 1 year and more than 80 will be able to carry out activities of daily living in the absence of heart failure symptoms, or with only minor symptoms.
2. In general, severe bleeding (affecting $\geq 50\%$ of HM II patients), localized infection not related to the VAD ($\geq 30\%$ of patients), and septicemia ($\geq 20\%$) are the principal complications in the first 30 days following implantation of a HM II device. During this period, there is also a risk of cardiovascular and cerebral complications such as serious arrhythmia ($>20\%$), right heart failure ($\geq 10\%$) and stroke ($\geq 10\%$). Beyond 1 month of VAD implantation, the incidence of infection related to the percutaneous driveline increases although this complication is a risk throughout the period of VAD support ($\geq 20\%$).
3. Important gaps are present in the current scientific literature. Despite the rapid evolution of continuous-flow VADs, the use of this relatively new technology is still generally limited. As a result, we consider the level of evidence regarding the effectiveness and safety of HM II based on the scientific literature published since 2008 to be moderate, since data arise from 1) a single randomized controlled trial (RCT) of relatively small size addressing one indication in comparison with a pulsatile-flow VAD; 2) a limited number of non-randomized controlled studies; and 3) several overlapping case series. We consider the level of evidence concerning HW to be very weak due to the extremely limited number of publications. There is a relative lack of information regarding long-term survival on support (>18 months after implantation for patients awaiting transplantation and >2 years for patients initially ineligible for transplantation), rates of readmission to hospital, costs related to complications, long-term end-organ function and quality of life of VAD patients.
4. The economic literature available on the cost-effectiveness of HM II (3 studies employing models) is unfavourable, regardless of the initial indication, according to a generally-accepted indicator (i.e., an incremental cost-effective ratio of $< \$50,000$ US per quality-adjusted life year gained). This is particularly the case for the use of a VAD as a bridge to transplant since this represents the addition of two expensive procedures, VAD implantation and cardiac transplantation; as well, the superior effectiveness of VADs compared to medical treatment implies that a greater proportion of VAD patients survive until transplantation and thus incur greater costs. However, these data should be interpreted in the context of an increasing lack of organ donors, poor effectiveness of the comparison medical treatment, the clinical reality of a choice between likely imminent death and survival, and the expected reduction in costs of VADs and technological improvement in the future as well as improved management of complications and increasing experience of expert VAD centres. It should be noted that the same cost-effectiveness threshold (using an incremental cost-effectiveness ratio, for example) does not necessarily have to be applied to all health interventions and decision contexts.

The following elements of a VAD program were consistently emphasized in the literature we consulted:

- Restriction of VAD implantation to authorized, equipped and experienced hospitals that meet strict organizational and expertise-related criteria;
- The need for a medico-surgical team with appropriate training and experience;
- The need for the pluridisciplinary team with expertise in the management of patients with severe heart failure to take into account the patient's global state and his/her preferences when discussing indications for possible use of long-term VAD support;
- The importance of careful selection of patients for mechanical cardiac support at the right time in the evolution of their heart failure;
- The need for regular follow-up of patients after VAD implantation and the recording of all implantations in a national/provincial registry, using a common reporting protocol for all centres involved.

As in the case of patients who receive a heart transplant, VAD patients must take multiple medications; maintain adequate doctor-patient relationships for long-term care; attend medical appointments; submit to frequent testing, clinical evaluations, and monitoring of cardiac function; be regularly assessed for the development of infections; and undergo rapid treatment for complications. They must also accomplish a number of technical tasks related to the VAD equipment (e.g. recognize and react to alarms, change batteries, carry out system tests, keep parts dry) and must avoid extreme movement and power surges. Cognitive ability, adaptive strategies and social support are thus very important.

There is a lack of information regarding the use of long-term implantable VADs by patients in Quebec and their clinical outcomes, both among those on the transplantation waiting list and those receiving the device as destination therapy. From 2006 to 2011, the mean waiting time for a heart transplant in Quebec varied from 6 months to 1 year. Such delay poses a risk of deterioration of clinical status that can lead to death or render transplantation impossible. A comparison of recent data on VAD use suggests that the current rate for Quebec (3.3 HM II devices implanted per million inhabitants) is higher than that in France, United Kingdom and Ontario, less than that in USA, and very similar to the rate in British Columbia. According to data available from one Quebec hospital, purchase of an HM II device (plus accessories) costs \$129,500 CAN. This implies a minimal purchase cost of \$3.9 million CAN for the implantation of 30 HM II devices (if the current number of implantations were to be maintained). The implantation of 60 HM II VADs, recommended in the RQCT report of 2010, implies a minimal cost of \$7.8 million CAN for device purchase alone, not considering the costs of patient evaluation, the implantation procedure, follow-up care and management of complications.

Given the aging of the Quebec population and the growing prevalence of heart failure, we expect the demand for both donor hearts and implantable VADs to increase. VADs will continue to capture the interest of the public and clinicians, particularly as device size decreases, ease of use, ease of implantation and durability increase, and when the entire apparatus, including the driveline and power source, can be implanted, greatly reducing the risk of infections.

Recommendations

Considering the present evaluation and discussion of the results with our scientific committee of Quebec physician-experts, INESSS makes the following recommendations. The bases for each recommendation are specified in brackets in Italics.

Context of use

- A long-term implantable VAD should be recognized as a therapeutic option that is complementary to heart transplantation for patients with end-stage chronic heart failure. Being eligible for a heart transplant should not be an essential criterion for VAD candidate selection. The medical team responsible for implantation should aim to choose the right patients at the right time in the evolution of their heart failure. Such candidates might be not eligible for a transplant at the time of VAD implantation, or their eligibility for a transplant might be uncertain (*clinical practice guidelines, HTA report, clinical studies, expert opinion*).
- A long-term implantable VAD should be considered a rare resource given the costs associated with its use for the public health care system in Quebec (*economic literature; expert opinion*). Thus, VAD use should be restricted at the provincial level.
- When resources are rare, it is appropriate according to the principle of equity and a utilitarian perspective to offer them to those patients most likely to benefit, and to avoid futile treatment. This applies to both long-term VADs (due to their cost) and to donor hearts (due to their scarcity). Clinical experts must assist governmental bodies with the development of criteria for use (*ethics literature, expert opinion*).

Structures, processes and organization of care

- The implantation of long-term VADs should only be performed in Quebec hospitals currently offering specialized cardiac transplantation services (*clinical practice guidelines, HTA report, expert consensus document, expert opinion*). These centres should have an efficient communication system with heart failure clinics in order to optimize care pathways along organized service corridors (*expert opinion*).
- Each ultraspecialized hospital should establish a pluridisciplinary team dedicated to implantation of long-term VADs and cardiac transplantation. This team should be comprised of cardiologists, cardiac surgeons and other medical specialists with heart failure expertise. It is also recommended that the following professionals be part of the team: a psychologist, a social worker, a biomedical engineer and specialists in palliative care, as well as an expert nurse specialized in mechanical cardiac support (*clinical practice guidelines, HTA report, expert consensus document, expert opinion*).
- It is important to ensure a certain uniformity in the types of professionals in each VAD team, and the development of a concretely collaborative approach between members that is supported by the hospital and recognized by each professional (*expert opinion*).
- The pluridisciplinary team should have administrative, financial and professional support regarding the process of patient evaluation, how to discuss therapeutic choices, and the relative weights to give to psychosocial factors, patient compliance, other comorbidities, and family/social support (*expert consensus documents, expert opinion*).

Patient selection

- Eligibility criteria for long-term VAD implantation that are clear, applicable and as objective as possible should be developed in a uniform manner by the ultraspecialized hospitals responsible for the VAD program (*ethics literature, expert opinion*).
- Candidates for long-term VAD implantation (HM II or similar device) should have a reasonable probability of a life expectancy of at least 2 years after the intervention (*clinical practice guidelines, HTA report, expert opinion*). There should also be a strong likelihood that quality of life will significantly increase after VAD implantation as a result of the patient's improved physical state.
 - More specifically, VAD eligibility should also depend on considerations other than clinical indications, such as the overall physical state of the patient, neurological and psychological status, availability of social support, access to medical services, preferences and patient compliance with treatment (*clinical practice guidelines, clinical studies, ethics literature, expert opinion*).
- It is necessary to periodically reassess indications for VAD use so that implantation is performed at the optimal time in the evolution of heart failure (*clinical practice guidelines, expert opinion*).

Ethical considerations and the patient's perspective

- It is essential to obtain fully informed consent from the patient before implantation of a long-term VAD, given the risks associated with the intervention and its potential burden for the patient, family and informal caregivers (*expert consensus document, ethics literature, expert opinion*). Informed consent implies the corollary of the patient's right to refuse VAD treatment.
 - There can be circumstances in which urgent VAD implantation is necessary. If a patient has not been previously evaluated for VAD use, implantation of a short-term device is preferred in order to allow for a complete evaluation and discussion of treatment options with the patient (*expert opinion*).
- Before VAD implantation, it is essential to establish a clear end-of-life care plan (known as "documented advanced care planning") and to discuss deactivation, explanation and/or non-replacement of the device (*clinical practice guidelines, ethics literature, expert opinion*).
- Before using a long-term VAD, a patient on a transplant waiting list should be informed that his/her priority on the list might change after implantation. Subsequent therapeutic decisions, including receipt of a donor heart, should relate to the patient's clinical needs (*HTA report, ethics literature, expert opinion*)

Economic considerations and budget implications

- The three ultraspecialized hospitals providing the VAD program, which serve the entire Quebec population, should have a dedicated budget that is adequate to ensure equitable access and the resources necessary for all program components (e.g. specialized personnel, intensive care beds, patient evaluation, follow-up medical care). It is reasonable that health regions transferring patients to these centres for VAD treatment should assume a portion of the costs (*clinical practice guidelines, expert opinion*).

Knowledge development

- A mandatory provincial registry of VAD use should be created in close collaboration with a representative committee of expert clinicians. Such a registry would assist in the monitoring of the VAD program and would provide data useful for updating indications as a function of needs, clinical outcomes, evolution of technology and resources. At the system level, such a registry could aid decision-making concerning reimbursement and the organization of care for patients with end-stage heart failure (*HTA report, expert consensus document, expert opinion*).
- In order to acquire more in-depth knowledge despite a relatively limited number of patients in Quebec, it is recommended that the provincial registry be either part of an interprovincial or international data collection or at least comparable to other registries regarding the definition of variables (*expert consensus document, expert opinion*).