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Neurological Events During Long-Term Mechanical Circulatory Support for Heart Failure

The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Experience

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Background—Progression of heart failure can lead to cardiac transplantation, but when patients are ineligible, long-term mechanical circulatory support may improve survival. The REMATCH trial showed that left ventricular assist devices (LVADs) prolonged survival in patients with end-stage disease, but with a significant number of adverse events. We report on the neurological outcomes in the REMATCH trial.

Methods and Results—We examined new neurological events in the 129 patients randomized to either LVAD placement (n=68) or medical management (n=61), classified as stroke, transient ischemic attack, toxic-metabolic encephalopathy, and other. There were 46 neurological events: 42 in 30 LVAD patients and 4 in 4 patients in the medical arm (χ^2 , 30/68 versus 4/61, $P<0.001$). Sixteen percent of the LVAD patients had a stroke, with a rate of 0.19 per year (95% CI, 0.10 to 0.33), many occurring in the postoperative period. The stroke rate in the medical arm was 0.052. A Kaplan-Meier survival analysis showed a 44% reduction in the risk of stroke or death in the LVAD group versus the optimal medical group ($P=0.002$). The mean interval from implantation to stroke was 221.8 days (± 70.4 days). History of stroke, age, and sepsis were not stroke risk factors in the LVAD group.

Conclusions—Fewer than half of the patients in the LVAD group had a neurological event, and there were few neurological deaths. Survival analysis combining stroke or death demonstrated a significant benefit for long-term circulatory support with an LVAD over medical therapy. Future trials will need to address prospectively all neurological outcomes, including neurocognitive function, and the role of long-term neuroprotection. (*Circulation*. 2004;109:2423-2427.)

Key Words: heart-assist device ■ stroke ■ heart failure

As the major indication for cardiac transplantation, heart failure affects an estimated 4.7 million Americans,¹ but the shortage of donor hearts limits the availability of this treatment option.² Ventricular assist devices (VADs) were originally used to provide mechanical circulatory support in patients awaiting planned heart transplantation. With the grave prognosis of end-stage heart failure on medical therapy and so few donor hearts at hand, the success of short-term bridge devices has led to clinical trials evaluating the suitability of VADs in patients not eligible for heart transplantation. The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) study was the first larger-scale, randomized trial demonstrat-

ing that long-term support with a left ventricular assist device (LVAD) could result in a substantial improvement in long-term survival in this population.³

Neurological events are among the most commonly reported complications after placement of LVADs.⁴ Cerebral embolism is the most frequent brain event, with reports ranging from 3% to 47%, but these events occurred largely in cases in which the device was used for a limited period of time as a bridge to heart transplantation.⁵⁻⁹ The use of textured blood-contacting surfaces in devices may result in a lower incidence of neurological events.^{9,10} The patients enrolled in REMATCH, however, had more severe disease and comorbidities, were older, and remained on device support

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longer than patients in other randomized trials for device treatment of heart failure.^{11,12} Therefore, the nature and extent of neurological complications of LVAD as a destination device in this population have yet to be fully defined. REMATCH was designed to enroll 140 patients and to continue enrollment until 92 deaths had occurred, and in our initial report of the outcomes, we reported that 10% of the patients in the LVAD arm had an ischemic stroke. We review here the neurological events in REMATCH patients, including an additional 61 patient-months of experience for the medical arm and 215 patient-months for the LVAD arm beyond those reported originally.

Methods

Patients and Procedures

As part of the REMATCH trial, 129 patients were randomized to either LVAD implantation (n=68) or optimal medical management (n=61). All participants signed institution-approved informed consent. Eligible patients for REMATCH were adults with chronic end-stage heart failure, most of whom had symptoms of NYHA class IV disease, with some later-randomized patients with class III heart failure. The primary end point was all-cause mortality; otherwise, patients were followed up for a period of 24 visits, once every 28 days (672 days), which was a joint decision between the investigators and the NHLBI Data Safety and Monitoring Board, which had oversight over the trial. The initial entry criteria for REMATCH included either NYHA class IV symptoms for >90 days despite maximal medical treatment, including ACE inhibitor, diuretic, and digoxin, and maximal oxygen consumption of <12 mL · kg⁻¹ · min⁻¹ or “continued need for” intravenous inotropic therapy. Inotrope dependence was initially defined as symptomatic hypotension, decreasing renal function, or worsening pulmonary congestion. It was later further defined as requiring evidence of 2 failed weaning attempts. Complete inclusion and exclusion criteria and details of IRB-approved, written informed consent are described elsewhere.^{3,13} Adverse events, including neurological events, were captured as secondary end points. All patients underwent administration of the NIH Stroke Scale¹⁴ at the time of study randomization in the hospital to quantify the nature and extent of previous neurological deficits, with higher scores denoting worse clinical states. A neurological event was defined as any new, temporary or permanent, focal or global neurological deficit ascertained in an examination by a neurologist using the NIH Stroke Scale and centrally adjudicated by a 5-member, independent committee of experts, which included a stroke neurologist, reporting to the National Heart, Lung, and Blood Institute of the US National Institutes of Health. Subsequently, all adjudicated neurological events were subdivided into 4 subcategories. A *stroke* was a focal ischemic or hemorrhagic brain event with signs and symptoms lasting >24 hours; a *transient ischemic attack* (TIA) was a focal ischemic brain event lasting <24 hours with a negative brain image, if one could be obtained; *toxic-metabolic encephalopathy* was a global change in mental status arising from organ or system failure; and *other* included miscellaneous conditions such as brain abscess, neurodegenerative disease, etc. Strokes and events subclassified as “other” were categorized as permanent deficits. A transient deficit consisted of the TIAs and toxic-metabolic encephalopathy because the latter was usually reversible if the underlying systemic condition was successfully treated. If a patient had a seizure judged to be caused by a toxic-metabolic disorder, then the event was considered to be in the toxic-metabolic category. Following the general principles of the REMATCH trial design, events were assigned to the LVAD or medical arm on an intent-to-treat basis.

Results

There were 46 neurological events in this trial. Forty-two events occurred among 30 of the LVAD patients, and 4

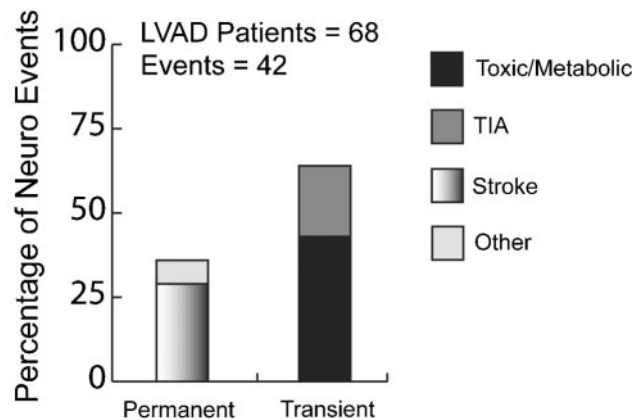


Figure 1. Relative proportion of transient and permanent neurological deficits among 68 patients in group that received LVAD.

events were documented among 4 patients in the medical management arm. Thus, patients in the LVAD arm were significantly more likely to suffer an adverse neurological event than those in the medical arm. (χ^2 , $P<0.001$). Figure 1 shows the distribution of these events among the LVAD patients in the 4 predefined categories: TIA, toxic-metabolic, other, and stroke. Approximately two thirds of these neurological episodes were transient, and one third were considered permanent. There were 12 strokes that occurred in 11 patients: 10 cerebral infarctions and 2 hemorrhages. Thus, 16% of all the LVAD patients had a stroke during their participation in this trial. The event rate for a permanent neurological deficit in the LVAD arm was 0.23 per patient-year (95% CI, 0.13 to 0.38), with a stroke rate of 0.19 per year (95% CI, 0.10 to 0.33). In contrast, the stroke rate in the medical management arm was 0.052. The cause of the stroke events was determined by reviewing the reports of radiographic images after strokes but not by the actual films. In the instances of nonhemorrhagic strokes, all were consistent with embolism except for border-zone infarction in one of the air emboli cases. The air emboli cases occurred because of a device failure (diaphragm rupture) and after inflow-graft repair. Four of the stroke events were adjudicated to have led to cerebrovascular death, with 2 such events occurring within the initial 30 days after LVAD implantation. None of the neurological events in the medical arm were adjudicated to have been the cause of death. Both cerebral hemorrhages in the LVAD arm were fatal. Neither of the 2 strokes in the medical management arm, 1 ischemic and 1 hemorrhagic, caused death. The “other” neurological events included focal brain infection, bilateral tremor, and new onset of dementia.

We performed a Kaplan-Meier analysis to determine whether an end point that combined stroke or death would alter our original finding of a survival benefit to the LVAD group (Figure 2), reflecting the view that patient outcomes should include major causes of disability. There was a 44% reduction in the risk of either stroke or death in the LVAD group compared with optimal medical therapy (95% CI, 18% to 68%; $P=0.002$). The average follow-up time for patients in the LVAD arm was 341.3 days, and for the medical arm, 226.3 days.

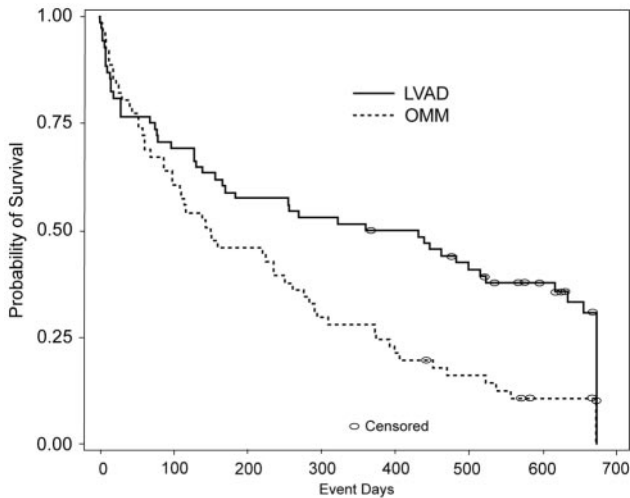


Figure 2. Kaplan-Meier analysis of stroke-free survival in LVAD group and group that received optimal medical therapy (OMM). Follow-up took place for 672 days. Circles depict censored patients whose follow-up was <672 days.

Several analyses were performed to determine whether there were specific risk factors that were associated with the occurrence of stroke in the LVAD group. With regard to previous neurological events, 9 of 61 of the patients in the medical management arm had a previous stroke, ascertained as part of the medical history without need of documentation, and 8 of 68 of the patients in the LVAD group entered our study with a previous stroke. The mean baseline scores on the NIHSS, assessing previous neurological injury, were 0.46 (SD, 1.18) for the medical management group and 0.81 (SD, 1.66) for the LVAD group, which was not significantly different (*t* test, $P=0.17$). None of the 9 patients with previous stroke in the medical arm had a postrandomization neurological event. Three of the 8 LVAD patients with a previous brain infarct experienced a stroke subsequent to device implant. Unfortunately, we were unable to have the NIH Stroke Scale administered at the time of a clinical event or at future follow-up. We also could not obtain CT images for formal adjudication as to stroke subtype, arterial territory, lesion location, and infarct size. A linear logistic regression analysis showed that increasing age was not a risk factor for stroke in the LVAD group ($P=0.83$).

Figure 3 shows the Kaplan-Meier actuarial stroke-free curve among patients in the device group. The mean interval from implantation to stroke was 221.8 days (± 70.4 days). There were 5 events within the first 30 days after implantation, but only 1 event from day 91 to day 480. Among the 68 patients who received the LVAD, there were 21 device replacements, after which 3 patients experienced a subsequent stroke. These 3 patients were stroke free from the time of the initial implantation until the replacement surgery, which was 358 days, 461 days, and 504 days, respectively. One patient had a cerebral ischemic event on the same day as implantation of the replacement LVAD. The other 2 patients had embolic strokes at 68 and 160 days, respectively, after they received the new device. There was 1 patient, randomized to the medical management arm, who crossed over to the

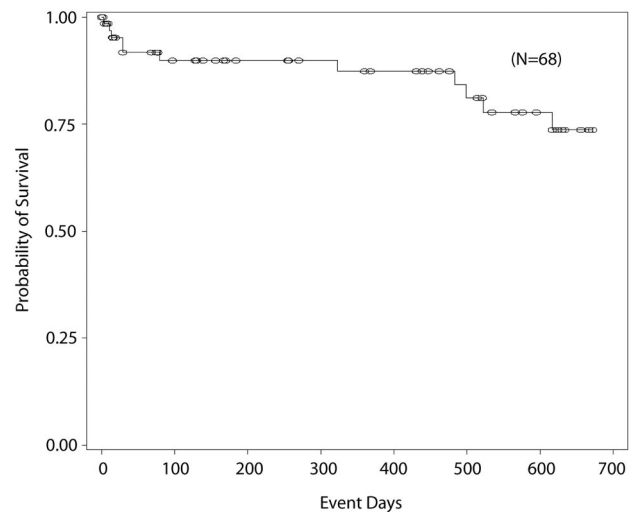


Figure 3. Kaplan-Meier analysis of time to stroke in LVAD group. Patients who died are censored.

LVAD group (implantation on day 280) and then had a stroke 112 days later. Because our analysis was based on intent to treat, his event was attributed to the original treatment assignment.

There was no recommended antithrombotic protocol in REMATCH involving either anticoagulation or antiplatelet therapy. Decisions about such management were entirely up to the local clinical site. In the LVAD group, 49 patients were documented to be taking antiplatelet medication on at least 1 of the scheduled 30-day follow-ups, and 26 patients were on anticoagulation on at least 1 follow-up. Among the 11 patients who had a stroke in the LVAD arm, 2 were taking warfarin and an antiplatelet agent at the monthly follow-up visit before their events, 1 of whom suffered a fatal stroke from air emboli, and 5 patients were taking only antiplatelet medication.

We reported previously that sepsis was common among LVAD patients, defined as a systemic response to serious infection, usually manifested by fever, tachycardia, tachypnea, and leukocytosis, which did not have to be associated with a localized site of infection.¹³ Because of recent data suggesting the association of inflammation and stroke risk,^{15,16} we explored whether different kinds of infection predicted neurological events. There was no statistically significant relationship between the presence of sepsis, device-related (percutaneous site or pocket) infection, or non-device-related infection (eg, urinary tract, sinus infection, yeast infection) at any time and stroke.

Discussion

Neurological events in REMATCH constituted a significant proportion of adverse events in patients with destination LVAD, with 44% sustaining at least 1 event and 16% having either an ischemic or hemorrhagic stroke. Approximately two thirds of these events were transient in nature (TIA or toxic metabolic), and one third were classified as permanent. The stroke rate from any cause was somewhat higher in the present analysis than the 10% reported previously,³ because

we had the subsequent opportunity to follow up every patient until the earlier occurrence of either death or 672-day survival. Nevertheless, a revised survival analysis that combined stroke or death still demonstrates a significant benefit for long-term circulatory support with an LVAD over medical therapy.

All previous data on the neurological complications of LVADs have been derived from the study of patients who received temporary circulatory support as a bridge to heart transplantation. The stroke rates in these studies have been extremely variable,^{4,9,17-22} but these reports are difficult to compare, because most are retrospective analyses of non-standardized, clinical examinations in which patients were implanted with different devices. The applicability of neurological outcomes of "bridge" studies to the results from REMATCH, however, may not be appropriate for several other reasons. First, none of our patients were eligible for cardiac transplantation. In addition to NYHA class IV heart failure, patients could have insulin-dependent diabetes with end-organ damage, chronic renal failure with a sustained serum creatinine of <3.5 mg/dL, or significant comorbidities such as obesity with a body mass index of not more than <40 kg/m² or fixed pulmonary hypertension with a pulmonary vascular resistance of <8 Wood units. Whereas the mean ages for patients implanted with bridge devices have ranged from 41 to 53 years,^{17,20} the mean age for patients in REMATCH was >66 years. The mean duration of circulatory support in the patients receiving an LVAD as a bridge to transplantation has ranged from 18 days¹⁷ to 165 days.¹⁹ In contrast, the period of device support was much longer in REMATCH, with more than half of patients surviving >1 year on continued support.

Congestive heart failure ranks second after atrial fibrillation as a risk factor in cardiogenic stroke,²³ with most strokes cardioembolic in origin.²⁴ Our baseline data were consistent with this elevated risk, showing that 14.7% of the patients in the medical treatment arm had a stroke at some time before randomization and 11.7% of those assigned to receive the LVAD had a previous stroke. Most studies have found that previous stroke carries significant risk for recurrence.^{25,26} Even though patients in both treatment groups in REMATCH were at high risk for primary and secondary stroke events, those given the LVAD were much more likely to have a neurological event in general and a stroke specifically. Other risk factors for stroke, such as age and the presence of focal or systemic infection, did not show expected associations. We were unable to evaluate the potential role of atrial fibrillation, because our data collection did not separate dysrhythmia subtypes. Future research will have to determine the relative effects of cardiac surgery, the device, or the greater opportunity to have events in patients who survive longer.

There were no protocol guidelines with regard to anti-thrombotic therapy, in part because of concern over internal bleeding, and the previous experience with this device in the transplantation-eligible population not using anticoagulation had shown few clinically apparent, thromboembolic events (2.7%).⁹ Moreover, a subset of these bridge patients underwent transcranial Doppler studies of the middle cerebral arteries during LVAD support, detecting a mean of 0.52 high-intensity

transient signals per 30-minute session. The patients enrolled in REMATCH, however, had more severe disease and comorbidities, were older, and most significantly, remained on device support longer than those in the bridge study. Although approximately half of the events in REMATCH occurred within the initial 30 days after implantation of either the initial or replacement device, the remaining strokes occurred from days 68 to 482. The bimodal occurrence of strokes over time in REMATCH suggests the possibility that there may be multiple pathophysiological mechanisms that might require different treatments. Unfortunately, we were unable to collect follow-up NIH Stroke Scale data or the brain images for the patients who had stroke after LVAD implantation, and so we did not have information about syndrome severity, stroke subtype, arterial territory, lesion location, and infarct size from which stroke mechanism might be inferred. Future research will need to have systematic collection of these stroke features so that we can better characterize the nature of these events. Additional research will have to determine the point after which the risk of hemorrhage is sufficiently reduced to permit safe treatment with traditional anticoagulants and whether novel approaches to anticoagulation might be suitable in the acute and post-acute implantation period.^{10,27}

Our study represents a starting point in the analysis of neurological complications in patients with long-term circulatory support for heart failure. There were only 129 patients in REMATCH, of whom 68 received the device. Although the device group clearly had more events, including stroke, the trial was not designed to have enough statistical power for analysis of specific risk factors. Our data addressed only outcomes from transplantation-ineligible patients receiving the HeartMate vented electric device (Thoratec). Future studies will determine the neurological outcomes from other devices providing long-term left ventricular assistance. Our patients were extremely sick with end-stage disease; how a younger, less sick population who might not otherwise qualify for transplantation might fare is not known. To make possible the future comparison of brain events across studies, there needs to be prospective measurement of neurological function using standardized instruments and event definitions at an appropriate baseline, at prescribed intervals, and at the time of new events. Neurological assessment also includes the specialized evaluation of neurocognitive function beyond that surveyed in instruments such as the NIH Stroke Scale, because its emphasis is primarily on motor and sensory function,²⁸ and embolic stroke in the setting of heart failure may lead to significant cognitive loss.^{29,30} Moreover, neurocognitive dysfunction can occur in heart failure in the absence of clinically obvious stroke, resulting in significant disability.³¹ Collection of neurological events in databases such as the ISHLT Mechanical Support Device Registry³² in conjunction with prospective studies will lead to a further understanding of LVAD-associated neurological events and a reduction of their incidence.

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