

QUESTION

Should advanced heart failure treatments (LVAD/HTx) vs. supportive care be used for patients with advanced heart failure with Friedreich ataxia?

POPULATION: patients with advanced heart failure with Friedreich ataxia

INTERVENTION: advanced heart failure treatments (LVAD/HTx)

COMPARISON: supportive care

MAIN OUTCOMES: Mortality - survival; Morbidity - quality of life;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>People with FRDA are at higher risk of advanced HF (Tsou et al, 2011).</p>	<p>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of the topic. 6 out of 7 indicated the consequences of heart failure was serious; 1 individual indicated it was probably serious. 6 out of 7 individuals indicated management of heart failure was urgent; 1 individual indicated it was probably urgent etc. 6 out of 7 indicated heart failure was a priority; 1 indicated it was probably a priority. (July 2020)</p>

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE					ADDITIONAL CONSIDERATIONS										
<ul style="list-style-type: none"> <input type="radio"/> Trivial <input type="radio"/> Small <input type="radio"/> Moderate <input type="radio"/> Large <input checked="" type="radio"/> Varies <input type="radio"/> Don't know 	<table border="1"> <thead> <tr> <th rowspan="2">Outcomes</th> <th rowspan="2">No of participants (studies) Follow-up</th> <th rowspan="2">Certainty of the evidence (GRADE)</th> <th rowspan="2">Relative effect (95% CI)</th> <th colspan="2">Anticipated absolute effects* (95% CI)</th> </tr> <tr> <th>Risk with supportive care</th> <th>Risk difference with advanced heart failure treatments (LVAD/HTx)</th> </tr> </thead> <tbody> <tr> <td>Mortality - survival</td> <td>4 (2 observational)</td> <td>⊕○○○ Very low^a</td> <td>-</td> <td colspan="2">Case series describing heart failure treatment of three individuals with FRDA. 1) 5 y.o. presenting with severe myocarditis</td> </tr> </tbody> </table>	Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Risk with supportive care	Risk difference with advanced heart failure treatments (LVAD/HTx)	Mortality - survival	4 (2 observational)	⊕○○○ Very low ^a	-	Case series describing heart failure treatment of three individuals with FRDA. 1) 5 y.o. presenting with severe myocarditis		<p>Consider additional diagnoses in heart failure patients with FA (ie myocarditis)</p>
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and experienced cardiac arrest. Underwent biventricular assist device placement and heart transplant. Postoperatively suffered a stroke with full recovery. Cardiac function remained stable 19 years post-transplant. 2) 42 y.o. diagnoses with heart failure at age 27, with EF of 5%. Automated implantable cardioverter-debrillator placed at age 33, age 35 placement of left ventricular assist device and at age 35 recieved a heart transplant with a permanent pace maker two weeks later due to a junctional rhythm. Cardiac function remained stable 5 years post-transplant. 3) 31 y.o. diagnosed with dilated cardiomyopathy. At age 37 patient required AICD placement and heart transplant. Cardiac function remained stable 8 years post-transplant. (McCormick et al 2017).

Case study describing a heart transplant in a 23 year old woman with FRDA. Progressive heart failure developed at age 21 (dilated cardiomyopathy, frequent hospitalisations). Following heart transplant, post-operative course was uneventful and allograft function remained without rejection with preserved function at 100 months. Neurological status improved, subject also delivered healthy child, with cardiac and neurological function remaining stable. (Ivak et al 2016).

Morbidity - quality of life - not measured	-	-	-	-	-
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1. McCormick A., Shinnick J.,Schadt K. et al. Cardiac transplantation in Friedreich Ataxia: Extended follow-up. Journal of the Neurological Sciences; 2017.
2. Ivak P, Zumrova A,Netuka I. Friedreich's ataxia and advanced heart failure: An ethical conundrum in decision-making. Journal of Heart and Lung Transplantation; 2016.

a. One case series with n=3. Potential for reporting of surviving patients only.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE					ADDITIONAL CONSIDERATIONS																		
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Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● Very low ○ Low ○ Moderate ○ High ○ No included studies 	There is ver low certainty of evidence as per the evidence profile table.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS						
<ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability 	<table border="1"> <thead> <tr> <th>Outcomes</th> <th>Importance</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Outcomes	Importance	Certainty of the evidence (GRADE)				
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<ul style="list-style-type: none"> ● No important uncertainty or variability 	Mortality - survival	CRITICAL ^a	⊕○○○ VERY LOW ^b
	Morbidity - quality of life - not measured	CRITICAL ^c	-

a. Identified as critical (4/6), important (1/6) and low importance (1/6) by people with FA and critical by expert authors on this topic.

b. One case series with n=3. Potential for reporting of surviving patients only.

c. Identified as critical (3/6), as important (2/6) and low importance (1/6) by people with FA and important by expert authors on this topic.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know 		<p>We are advocating for CONSIDERATION of advanced HF therapies based on individual circumstances.</p> <p>Diagnosis of FA alone should not preclude such considering advanced HF therapies.</p>

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know 	No published evidence available.	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if the intervention was reasonable (weighing up the balance between benefits, harms and costs). 1 out of 3 individuals indicated management with advanced heart failure treatments was reasonable; 1 out of 3 probably reasonable and 1 out of 3 not reasonable. (August 2020)

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention <input type="radio"/>	Conditional recommendation against the intervention <input type="radio"/>	Conditional recommendation for either the intervention or the comparison <input type="radio"/>	Conditional recommendation for the intervention <input checked="" type="radio"/>	Strong recommendation for the intervention <input type="radio"/>
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CONCLUSIONS

Recommendation

Advanced heart failure therapies such as a left ventricular assist device, implantable cardioverter-defibrillator, biventricular pacemaker and heart transplantation should be considered for individuals with Friedreich ataxia and heart failure, based on consideration of both their cardiac and overall health status.

Justification

Based on the current evidence, advanced heart failure therapies should be considered based on individual circumstances. A diagnosis of FRDA alone should not preclude such consideration. Evidence from case reports indicates positive outcomes (Yoda et al, 2016; Ivak et al, 2016; Yoon et al, 2012; Segovia et al, 2001; Sedlak et al, 2004; Leonard et al, 2001).

Subgroup considerations

This recommendation is for individuals with Friedreich ataxia with a reduced left ventricular ejection fraction (i.e. <55%).

Research priorities

Reference

Ivak P, Zumrova A, Netuka I. Friedreich's ataxia and advanced heart failure: An ethical conundrum in decision-making. *J Heart Lung Transplant.* 2016;35(9):1144-5.

Leonard H, Forsyth R. Friedreich's ataxia presenting after cardiac transplantation. *Arch Dis Child.* 2001;84(2):167-8.

Sedlak TL, Chandavimol M, Straatman L. Cardiac transplantation: a temporary solution for Friedreich's ataxia-induced dilated cardiomyopathy. *J Heart Lung Transplant.* 2004;23(11):1304-6.

Segovia J, Alonso-Pulpon L, Burgos R, Silva L, Serrano S, Castedo E, et al. Heart transplantation in Friedreich's ataxia and other neuromuscular diseases. *J Heart Lung Transplant.* 2001;20(2):169.

Tsou AY, Paulsen EK, Lagedrost SJ, Perlman SL, Mathews KD, Wilmot GR, et al. Mortality in Friedreich ataxia. *J Neurol Sci.* 2011;307:46-9.

Yoda M, El-Banayosy A, Arusoglu L, Tendrich G, Minami K, Korfer R. Permanent use of a ventricle assist device for dilated cardiomyopathy in Friedreich's ataxia. *J Heart Lung Transplant.* 2006;25(2):251-2.

Yoon G, Soman T, Wilson J, George K, Mital S, Dipchand AI, et al. Cardiac transplantation in Friedreich ataxia. *J Child Neurol.* 2012;27(9):1193-6.