QUESTION

Should insulin alone vs. metformin or novel glucose-lowering therapy (e.g., SGLT2i, GLP1RA, DPPIVi) be used for initial therapy for adults with lower-risk diabetes mellitus (HbA1c <8.5%, no ketones, no acute hyperglycaemia) with Friedreich ataxia?	
POPULATION:	initial therapy for adults with lower-risk diabetes mellitus (HbA1c <8.5%, no ketones, no acute hyperglycaemia) with Friedreich ataxia
INTERVENTION:	insulin alone
COMPARISON:	metformin or novel glucose-lowering therapy (e.g., SGLT2i, GLP1RA, DPPIVi)
MAIN OUTCOMES:	Diabetes control/complications; Acute care utilization; Disease progression; Health-related quality of life;
BACKGROUND:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of diabetes mellitus. 5/7 indicated that the problem was serious, 1/7 indicated probably serious, 1/7 indicated they didn't know if serious. 3/7 indicated that the problem was urgent, 2/7 indicated probably urgent, 1/7 indicated probably not urgent, 1/7 indicated they didn't know if urgent. 2/7 indicated that the problem was a priority, 4/7 indicated probably a priority, 1/7 indicated they didn't know if priority. (Aug 2020)

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	A search of three databases (CENTRAL, MEDLINE, EMBASE) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 15 July 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	A search of three databases (CENTRAL, MEDLINE, EMBASE) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 15 July 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	No published evidence.	

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability		

Outcomes	Importance	Certainty of the evidence (GRADE)
Diabetes control/complications - not measured	CRITICAL[a]	-

Acute care utilization - not measured	CRITICAL[b]	-
Disease progression - not measured	IMPORTANT[c]	-
Health-related quality of life - not measured	IMPORTANT[d]	-

a. Identified as critical (4/6), important (1/6) and low importance (1/6) by people with FA and important by expert authors on this topic.
b. Identified as critical (3/6), important (2/6) and low importance (1/6) by people with FA and critical by expert authors on this topic.
c. Identified as critical (1/6), important (4/6) and low importance (1/6) by people with FA and critical by expert authors on this topic.
d. Identified as critical (2/6) and important (4/6) 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
○ 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	No published evidence.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	No published evidence.	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if using insulin alone for initial therapy for adults with less severe diabetes was acceptable (weighing up the balance between benefits, harms and costs). 1/3 indicated the intervention varied or was sometimes

		acceptable, 2/3 indicated they didn't know if acceptable. (Aug 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	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

There is insufficient evidence to favor either insulin alone or metformin or novel glucose-lowering therapies (e.g., SGLT2i, GLP1RA, DPPIVi) as initial therapy for adults with lower-risk diabetes mellitus (HbA1c < 8.5%, no ketones, no acute hyperglycemia) with Friedreich ataxia.

We suggest an individualized approach with either insulin alone, and/or a glucose lowering agent, with the choice of medication patient dependent, particularly because of the heterogeneity in FRDA-related DM.

Justification

While there is little data in FRDA associated DM, we suggest following adult guidelines for type 2 diabetes which indicate that first line therapy should depend on comorbidities and patient-centered treatment factors (American Diabetes Association, 2021; American Diabetes Association, 2022; Cosentino et al, 2020; Garber et al, 2020; Mayer-Davis et al, 2018). Additionally, metformin is used in some individuals with FRDA (McCormick et al, 2017). There are concerns related to metformin (inhibition of complex I and risk of lactic acidosis) but one study did not find increased metformin-related cell death in FRDA cells (Ailts et al, 2019; Cameron et al, 2018). There are possible benefits, particularly cardiac benefits, from GLP-1 agonists but these have not been specifically tested in FRDA (Igoillo-Esteve et al, 2019; Marso et al, 2016).

In the general population, there are benefits related to heart failure from SGLT-2 inhibitors (McMurray et al, 2019), but this has not been tested in FRDA. If one were to utilize a SGLT-2 inhibitor, ketone monitoring and close-follow up with endocrinology based on risk of euglycemic DKA is necessary (Rosenstock et al, 2015).

Despite limited data, in other mitochondrial disorders consideration of GLP-1agonists or SLGT-2 inhibitors has been recommended by some clinicians, due to favorable cardiac and renal profiles (Yeung et al, 2020).

Subgroup considerations

This recommendation is for adults with Friedreich ataxia with lower risk diabetes mellitus (HbA1c <8.5%, no ketones, no acute hyperglycemia).

Research priorities

Research priorities include addressing which anti-diabetic agent should be used initially and evaluating specific benefits and risks related to FRDA-related DM.

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