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Factors associated with favorable 5 year outcomes in islet transplant alone recipients with type 1 diabetes complicated by severe hypoglycaemia in the Collaborative Islet Transplant Registry

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Factors associated with favourable 5 year outcomes in islet transplant alone recipients with type 1 diabetes complicated by severe hypoglycaemia in the Collaborative Islet Transplant Registry

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What is relevant?

1. **Lack of large pediatric cohorts** in recent publications on islet transplantation
2. Benefits of islet transplantation alone in **adult** patients with type 1 diabetes (complicated by severe hypoglycemia)
3. Identification of **4 factors associated with favourable 5 year outcomes** after islet transplantation
4. 3 out 4 factors **are not directly related to patient age**
5. Lessons learnt from large adult transplant cohort could serve pediatric patients
6. Incl. teenagers in comparable clinical setting

Methods I

1. Based on data from the Collaborative Islet Transplant Registry (CITR), the largest collection of human islet transplant data in the world

2. Retrospective analysis included 398 individuals with type 1 diabetes and at least 1 severe hypoglycaemic events (SHE) who received an allogeneic islet transplant alone (ITA) between 1999 and 2015

Methods II

3. Outcomes analyzed:

1. HbA1c <53 mmol/mol (7.0%) and absence of SHEs	4. Fasting C-peptide ≥0.1 nmol/l
2. HbA1c <53 mmol/mol (7.0%)	5. Fasting glucose of 3.3–7.8 mmol/l
3. Absence of SHEs	6. Insulin independence

4. Serious advers events (SAE) related to islet product/infusion procedure or to the immunosuppression regimen

5. Univariate analysis and multivariate analysis to identify predictors associated with the highest prevalence of successful study outcomes across all the outcomes investigated

Baseline characteristics of study cohort

Patient characteristics
Mean ± SD age was 46 ± 10 years with 30 ± 11 years of diabetes
0.53 ± 0.18 U/kg daily insulin usage
9.4 ± 4.8 mmol/l fasting glucose
61.5 ± 13.9 mmol/mol HbA1c (7.8 ± 3.4%).

Immunosuppression
54% received induction regimens that included TCD antibodies and/or TNF-α inhibition and
78% were maintained on regimens of calcineurine and mechanistic target of rapamycin (mTOR) inhibition

Islet preparations
Mean ± SD cold ischemia time was 7.7 ± 4.7 h and culture time was 20.5 ± 16.7 h (which included 19% not cultured)
Mean ± SD total IEQs infused over one to six infusions was 863,000±395,000

Results: The common favourable factors (CFF)

Four factors were strongly associated with higher prevalence (≥10%) across all the desired outcomes of islet transplantation:

- Recipient age ≥35 years
- Total of ≥325,000 IEQs infused over one to several infusions
- Induction with TCD antibodies and/or TNF-α inhibition
- Maintenance with calcineurine inhibitosr (CNI) and mTOR inhibitors (for at least some portion of follow-up)

Results: The common favourable factors (CFF)

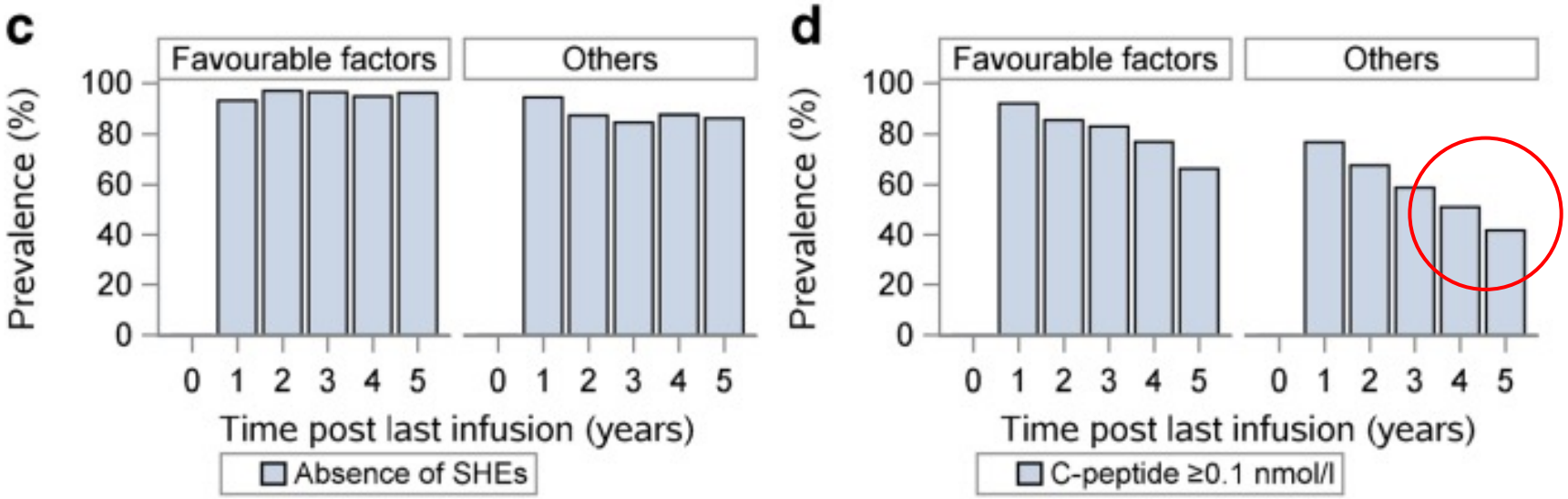
Presence of these 4 common favourable factors (4CFF) defines two subgroups:

4CFF (N=126) vs. **<4CFF** (N=272)

Main study outcomes I

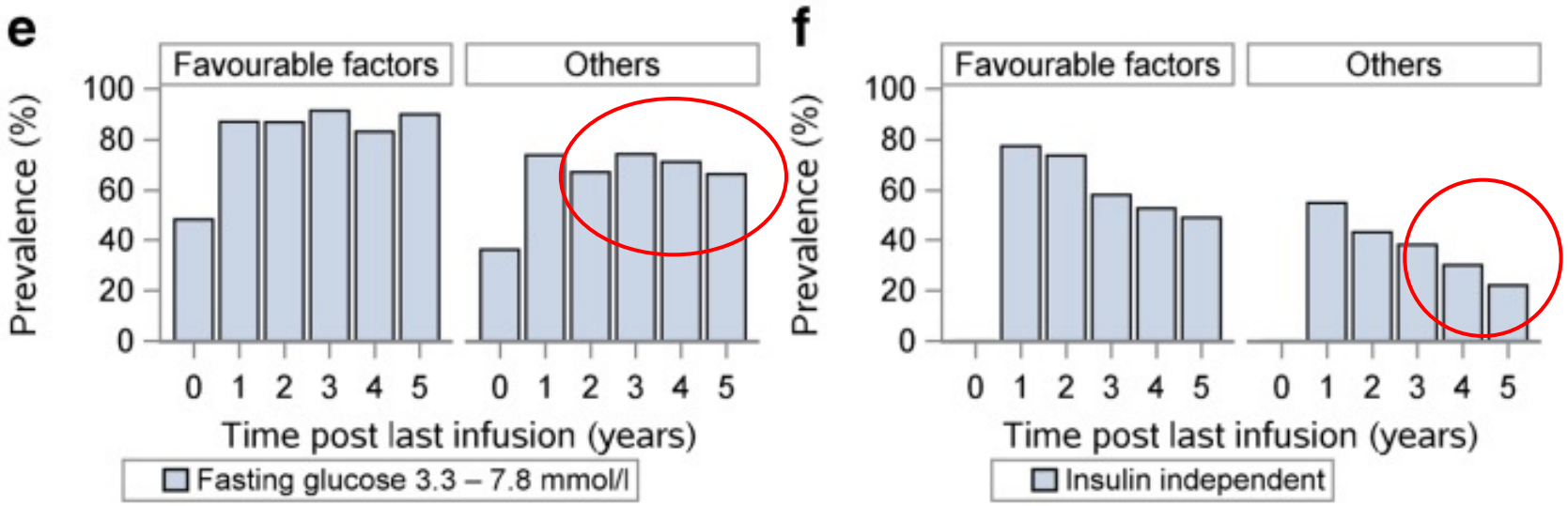
Observed prevalence rates of the study outcomes in the 4CFF subgroup (favorable factors, n=126) vs the <4CFF subgroup (others, n=272).

Main study outcomes II



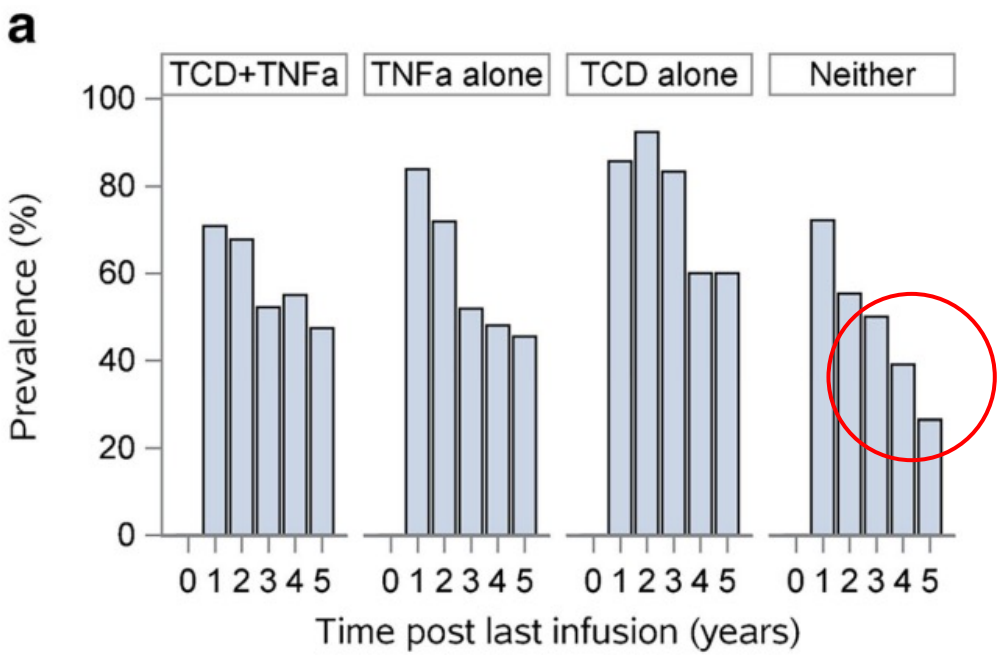
Observed prevalence rates of the study outcomes in the 4CFF subgroup (favourable factors, n=126) vs the <4CFF subgroup (others, n=272)

Main study outcomes III



Observed prevalence rates of the study outcomes in the 4CFF subgroup (favorable factors, n=126) vs the <4CFF subgroup (others, n=272)

Induction therapy and prevalence of insulin independence



Prevalence of insulin independence 1–5 years post last infusion

Maintainance immunosuppression

ESM Table 13. Prevalence of primary outcomes for subgroup with all 4 common favourable factors (left column)vs. common favourable factors except mTOR+CNI (right column).

	4CFF						4 Common Favourable Factors Except mTOR+CNI					
Outcome	**Base-line**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Base-line**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
HbA_{1c} <53 mmol/mol (7.0%) and Absence of SHEs	0%	83%	78%	77%	73%	73%	0%	63%	62%	59%	67%	57%
HbA_{1c} <53 mmol/mol (7.0%)	34%	86%	80%	81%	77%	76%	15%	66%	67%	68%	67%	59%
Absence of SHEs	0%	93%	93%	95%	94%	95%	0%	93%	95%	89%	90%	92%
C-peptide ≥0.1 nmol/l	0%	92%	86%	82%	75%	68%	0%	70%	72%	59%	56%	58%
Fasting Glucose 3.3- 7.8 mmol/l	48%	87%	85%	91%	82%	87%	35%	70%	64%	62%	75%	58%
Insulin Independence	0%	75%	71%	60%	56%	53%	2%	50%	38%	39%	36%	39%

Limitations

- Observational study with its limits (declining completeness of data with increasing length of follow-up)
- Incomplete data could have relevant impact on main findings and conclusions
- The predictors of outcome identified in ITA recipients may not be generalizable to other recipient categories e.g. pediatric patients

Conclusions

- Four factors associated with the highest rates of successful outcomes

- At 5 years after the last islet infusion 95% were
  - protected from severe hypoglycaemia
  - 76% had HbA1c <53 mmol/mol (7.0%)
  - 53% were insulin independent

- Low prevalence of immunosuppression-related serious adverse without complete recovery, disability or death

Conclusions

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  - protected from severe hypoglycaemia
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Possible consequences for daily pediatric practice

- Transfer of knowledge about clinical outcomes and benefits of induction therapy and long-term immunosuppressive therapy to pediatric patients

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