NEWS BRIEFING
Evolving Concepts in Type 1 Diabetes

Moderated by:
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Blood Pressure Thresholds for Optimal Cardiovascular Health in Type 1 Diabetes

1464-P

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Postdoctoral Fellow at the Center for Pharmaceutical Policy and Policy (CP3)
University of Pittsburgh

On behalf of Dr.’s Maria M. Brooks, Matthew F. Muldoon,
Tina Costacou and Trevor J. Orchard
Cardiovascular Disease (CVD) Burden in Type 1 Diabetes

CVD is the **leading cause** of premature mortality in type 1 diabetes.

CVD risk is particularly high **at younger age** in type 1 diabetes:

- CVD occurs **10 to 15 years earlier**
- Young adults with type 1 diabetes have recently been shown in three studies to be **over 20-30 times more likely** to die from heart disease.
Current blood pressure target guidelines for type 2 and type 1 diabetes

ADA 2019:

- 140/90 mmHg (10-year CVD risk < 15%) or
- 130/80 mmHg (Existing CVD or 10-year CVD risk > 15%)

“…Notably, there is an absence of high-quality data to guide blood pressure targets in type 1 diabetes…”

---ADA, Standards of Medical Care in Diabetes, 2019
Study objectives

• Determine optimal blood pressure thresholds associated with minimal coronary artery disease risk in young adults with childhood-onset type 1 diabetes

• Compare blood pressure and glucose in term of predicting coronary artery disease
Pittsburgh Epidemiology of Diabetes Complications (EDC) Study of Childhood-onset Type 1 Diabetes

Pittsburgh EDC Study participants without baseline heart disease

- N=605
- Baseline (1986-88) mean age=27 yrs, diabetes duration=19 yrs
- Follow up=25 yrs (2011-2014)
Coronary artery disease risk by different blood pressure levels

- We examined risk at systolic blood pressure (SBP) levels of 110, 120, 130, and 140 mmHg and diastolic blood pressure (DBP) at 60, 70, 80 and 90 mmHg

- Statistical analyses showed cut points of 120 mmHg for SBP and 80 mmHg for DBP best predicted risk
Risk stratification by time-weighted BP and time-weighted HbA1c

- **g1**: both good control (reference group)
- **g2**: high BP only, (BP > 120/80 mmHg)
- **g3**: high HbA1c only, (HbA1c > 8%)
- **g4**: both poor control, (BP > 120/80 mmHg and HbA1c > 8%)

Hazard ratio (95% CI)

- **g2 vs. g1**: 2.0 (1.04, 3.8)
- **g3 vs. g1**: 1.7 (0.99, 1.9)
- **g4 vs. g1**: 3.1 (1.7, 5.6)

Adjusted for age, gender, diabetes duration, and current use of antihypertensive medications, history of smoking, updated mean BMI, HDL and non-HDL cholesterol and raised albuminuria
Summary

In type 1 diabetes:

• Blood pressures greater than 120/80mmHg doubles the risk of heart disease

• High blood pressure and high glucose levels present similar risk for developing heart disease
Take-away message

• In type 1 diabetes, optimal blood pressure goals may be lower (e.g., 120/80mmHg) than currently recommended (i.e. 130-140/80-90)

• Young adults with type 1 diabetes should have careful monitoring of their blood pressure and, in the absence of direct trial data, our findings should be carefully considered when setting treatment goals
Type 1 diabetes and the developing brain: a longitudinal study of brain growth by the Diabetes Research in Children Network (DirecNet)

209-OR

Nelly Mauras, MD
Co-principal Investigator and Chief of the Division of Endocrinology, Diabetes & Metabolism, Nemours Children’s Health System, Jacksonville, Florida
Professor of Pediatrics, Mayo College of Medicine
Disclosures

• Device supply agreements
  • Medtronic

• Research Grant Support
  • Medtronic, NovoNordisk

• Research Supply agreement
  • Lifescan, Johnson & Johnson
Background

• Maintenance of near-normoglycemia in young children with diabetes is often limited by parental fears of the risks of hypoglycemia and impaired cognitive development.

• Human and experimental animal data suggest that both hyper- and hypoglycemia, depending on age and severity, can lead to altered brain structure and cognitive function, particularly in the young developing brain.
Primary Aims

• To investigate if there are differences in the brain of very young children with T1D as compared to control children without diabetes followed longitudinally over 5 years

• To correlate these neuroanatomical changes with long-term exposure to hypo- and hyperglycemia
T1 Diabetes and the brain in children: Longitudinal Study Design

**Baseline**                    **Time 3**
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<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Time 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with T1D</td>
<td>144</td>
<td>138</td>
</tr>
<tr>
<td>Age-matched controls</td>
<td>72</td>
<td>67</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>7 ± 1.7</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>Median diabetes duration (yrs)</td>
<td>2.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Mean HbA1C (%)</td>
<td>7.9 ± 0.9</td>
<td>8.0 ± 1.1</td>
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* Visit
  - HbA1C
  - CGM

Non sedated MRI
Cognitive test

- **1a**
- **2a**
- **3b**
- **4b**

Diagram notes:
- 0, 6, 12, 18, 54, 60, 66, 72, 78 months
- Visit
  - HbA1C
  - CGM

Notes:
- Non sedated MRI
- Cognitive test
Children with T1D had differences in gray matter volumes compared to controls.

Marzelli et al. Diabetes 2014
Longitudinal Brain Growth

Mauras et al. Diabetes 2015

P<0.001
**1346-P**

Longitudinal Evaluation of Cognitive Functioning in Young Children with T1D Showed Persistent Deficits on Full Scale and Verbal IQ and Vocabulary as Compared to Non Diabetic Controls, Differences Associated with Hyperglycemia

**1382-P**

Functional MRI Results Show Compensatory Brain Hyperactivation in Children With Type I Diabetes Compared to Controls
Summary & Conclusions

In very young children with type 1 diabetes we have observed:

• Significant differences in total brain and regional gray and white matter growth in widespread brain regions vs. controls.
• Differences are related to disease-long measures of dysglycemia.
• These data suggest that continued exposure to chronic hyperglycemia may be detrimental to the developing brain and cognition.
• Longitudinal follow-up of this cohort will better elucidate the brain’s developmental changes over time.
• Whether these apparent differences can be reversed with scrupulous metabolic control and automated insulin delivery systems is being actively investigated.
TrialNet
Predict and Prevent Type 1 Diabetes

Carla Greenbaum, MD
Director of Diabetes Research Program,
Benaroya Research Institute, Seattle WA
Disclosures

- Janssen Research and Development: Research Support
Type 1 Diabetes TrialNet

NIH funded, international research consortium of 25 Clinical Centers, multiple Affiliate Sites, Data Coordinating Center, Clinical Network Hub, Core Laboratories, Collaborative Mechanistic Studies Panel

Mission is to prevent type 1 diabetes and stop disease progression by preserving insulin production before and after diagnosis.

- Pathway to Prevention (natural history study) – screening and monitoring
- Intervention trials prior to diagnosis
- Intervention trials in new-onset T1D
- Mechanistic studies
The need for Disease Modifying Therapy: Insulin is Not Enough

- Decrease life expectancy even in those with good HbA1c
- Decrease life expectancy particularly in those diagnosed as children
- Severe hypoglycemia is frequent at all ranges of HbA1c
- Poor glucose control; getting worse despite increasing use and availability of technology

Lind et al, NEJM. 2014
Miller K et al, Diabetes Care 2015
Foster NC et al, DTT, 2019
Changing from treating symptoms to treating underlying disease
Example of juvenile idiopathic arthritis

Slide adapted from Daniel Lovell, MD
T1D Disease Modifying Immune Therapy

- Rituximab (anti-B cell)
- Abatacept (co-stimulation blockade)
- Alefacept (impact memory T cells)
- Teplizumab (anti-T cell)
- Anti-thymocyte globulin; ATG (anti-Tcell)

Haller MJ, Diabetes 2019
Can immune therapy delay clinical type 1 diabetes in at-risk individuals?

We **can** identify individuals before clinical diagnosis of type 1 diabetes

- TrialNet Pathway to Prevention study
- More than 200,000 family members of people with type 1 diabetes tested for autoantibodies
  – TrialNet.org
- 2.5% will have multiple antibodies
- Essentially all with multiple antibodies will eventually develop clinical diabetes
We **can** identify individuals before clinical diagnosis of type 1 diabetes.
TrialNet Portfolio: Disease Modifying Therapy
TrialNet Portfolio: Disease Modifying Therapy
TrialNet
Teplizumab for Prevention of Type 1 Diabetes in Relatives At-Risk

Kevan Herold, MD
Professor of Immunobiology and Internal Medicine
Yale University
Disclosures

- I have consulted for Provention Bio
- I have a patent on an assay to measure beta cell death
Background and rationale

• T1D is an immune mediated disease. Teplizumab (anti-CD3 mAb), an immune therapy, has been tested in 5 previous clinical trials in patients with clinical T1D and showed that treatment could preserve insulin secretion after clinical diagnosis.

• This trial was designed to determine whether teplizumab would delay the onset of individuals who were at very high risk for T1D.
Design and intervention

- **Design**: Randomized, placebo controlled study
- **Population**: Relatives of those with T1D with 2 or more autoantibodies and abnormal glucose tolerance.
- The majority of the participants (72%) were children. 64% were siblings of patients with T1D.
- **Therapy**: N=76 individuals randomized to 14 daily infusions of teplizumab (n=44) or placebo (n=32), as an outpatient.
- **Procedures**: The participants were followed by regular Oral Glucose Tolerance Testing to test for development of T1D
Results

• Teplizumab treatment delayed the diagnosis of T1D a median of two years later than those on placebo (i.e. 24 vs 48 mos after enrollment). This result was highly statistically significant.

• Over seven years, only 43% of teplizumab treated individuals developed diabetes compared to 72% of those treated with placebo.

• The annualized rate of diabetes was reduced from 35.9% to 14.9%.

• Adverse events including low white blood cells counts and rash were transient and similar to those previously reported.
Summary

• Non-diabetic relatives with multiple antibodies and abnormal glucose tolerance are at very high risk for progression to clinical T1D

• A single two-week treatment with teplizumab delayed the median time of onset of T1D by an average of 2 years

• The drug is effective in children and adults

• Teplizumab can be safely administered in children and adults who are at risk for T1D

• Subgroups of individuals, identified by characteristics at screening, may have particularly robust responses to teplizumab
Significance and Next Steps

• This is the first trial that met its clinical endpoint in delaying the onset of Type 1 diabetes

• The two year delay in diagnosis is clinically important.
  • In light of the daily burden of disease management, any time without clinical diabetes has significance, particularly for children who were about ¾ of the study participants

• We can accurately predict and now delay the onset of T1D

• TrialNet is testing other immune agents to determine their effect on delaying T1D. Relatives can be tested for risk through TrialNet.org.
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• Any reporters in violation of the embargo policy will be barred from this and future Scientific Sessions.

• For interviews with any of the presenters, please contact Michelle Kirkwood or a member of the Press Office team.
Media Contact

On-site Press Office – Room 314

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