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Health Outcomes in Device Studies

Comments for May 21, 2024 MEDCAC Meeting

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Disclosures

- I am an employee and shareholder of Dexcom, Inc

Trial Duration

Trial duration of 12 weeks is sufficient

- The DCCT conclusively demonstrated improvements in A1C resulted in reduced rates of microvascular complications in people with type 1 diabetes[1]
- UKPDS conclusively demonstrated improvements in A1C resulted in reduced rates of microvascular complications in people with type 2 diabetes[2]
- EDIC[3] & UKPDS Follow-up[4] demonstrated reduced risk of cardiovascular disease in people with type 1 & type 2 diabetes in intensively treated groups
- A1C is an appropriate surrogate marker for complications and can be assessed after 12 weeks
- Requiring trials longer than 12 weeks:
  - Increases participant burden and risk of increased drop out
  - Delays length of time for therapies to reach patients and would be prohibitively expensive
- **We recommend a minimum trial duration of 12 weeks**

Diabetes Care Volume 37, January 2014

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 Years: Overview

David M. Nathan, for the DCCT/EDIC Research Group*

DCCT/EDIC 30TH ANNIVERSARY

OBJECTIVE

The Diabetes Control and Complications Trial (DCCT) was designed to test the glucose hypothesis and determine whether the complications of type 1 diabetes (T1DM) could be prevented or delayed. The Epidemiology of Diabetes Interventions and Complications (EDIC) observational follow-up determined the durability of the DCCT effects on the more-advanced stages of diabetes complications including cardiovascular disease (CVD).

RESEARCH DESIGN AND METHODS

The DCCT (1982–1993) was a controlled clinical trial in 1,441 subjects with T1DM comparing intensive therapy (INT), aimed at achieving levels of glycemia as close to the nondiabetic range as safely possible, with conventional therapy (CONV), which aimed to maintain safe asymptomatic glucose control. INT utilized three or more daily insulin injections or insulin pump therapy guided by self-monitored glucose. EDIC (1994–present) is an observational study of the DCCT cohort.

RESULTS

The DCCT followed >99% of the cohort for a mean of 6.5 years and demonstrated a 35–76% reduction in the early stages of microvascular disease with INT, with a median HbA_{1c} of 7%, compared with CONV, with a median HbA1c of 9%. The major adverse effect of INT was a threefold increased risk of hypoglycemia, which was not associated with a decline in cognitive function or quality of life. EDIC showed a durable effect of initial assigned therapies despite a loss of the glycemic separation (metabolic memory) and demonstrated that the reduction in early-stage complications during the DCCT translated into substantial reductions in severe complications and CVD.

CONCLUSIONS

DCCT/EDIC has demonstrated the effectiveness of INT in reducing the long-term complications of T1DM and improving the prospects for a healthy life span.

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Clinical trial reg. nos. NCT00360815 and NCT00360893, clinicaltrials.gov.

*A complete list of participants in the DCCT/EDIC Research Group can be found in N Engl J Med 2011;365:2366–2376.

See accompanying articles, pp. 5, 8, 17, 24, 31, 39, and 44.

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A1c

0.3% difference is clinically meaningful

- Magnitude of A1c improvement is correlated with baseline A1c levels[1]
  - Lower baseline levels typically result in lower magnitude of improvements
- A1c change of 0.3% is clinically meaningful and has been associated with reduced risk of retinopathy[2]
- Guidance from both the FDA[3,4] and the European Medicines Agency (EMA)[5] use the 0.3% threshold when evaluating drugs to improve glycemic control
- **We recommend establishing a minimum clinically important difference for A1C of 0.3%**

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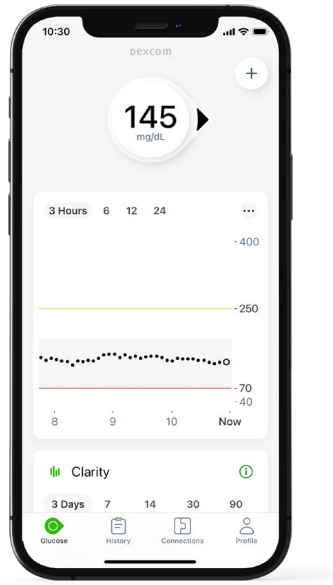
Time in Range (TIR)

5% difference in TIR is clinically meaningful

- CGM use allows for measurement of TIR, which has significant advantages over A1c[1]
- TIR derived from 7-point fingerstick testing in DCCT was strongly associated with the risk of microvascular complications[2]
- A 10% increase in TIR correlates with a 0.6-0.8% reduction in A1C[3,4]
- A 5% increase in TIR correlated with a significant reduction in risk of retinopathy[5]
- A 2019 international consensus statement on TIR concluded that “incremental successes (e.g., 5% increase in TIR) are, in fact, clinically significant”[6]
- A 2023 international consensus statement concluded that, “A difference of ≥5% (absolute percentage points) in time in range is considered clinically meaningful for an individual participant in a clinical study and 3% is considered clinically meaningful for a treatment group difference in mean time in range”[7]
- **We recommend establishing a minimum clinically important difference for TIR no higher than 5%**



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