Closer Look

MEMORANDUM

New UK NICE clinical guidelines recommend CGM for the first time in certain adults and children with type 1 diabetes - August 31, 2015

Executive Highlights

- The new UK NICE clinical guidelines published on Wednesday recommend CGM for the first time in certain adults and children with type 1 diabetes. Encouragingly, the criteria are not as onerous as we would expect, focusing on patients with lots of hypoglycemia.
- We hope the new policies meaningfully expand CGM uptake in the UK, and bode well for future coverage of automated insulin delivery.
- NICE has also released a new draft evaluation document on sensor augmented pump therapy. It recommends coverage of the Medtronic Veo for patients with frequent severe hypoglycemia, or those facing anxiety about such episodes. It does not recommend coverage of the Animas Vibe, citing lack of evidence.

In a major reimbursement victory for diabetes technology, the new UK NICE clinical guidelines published on Wednesday recommend CGM for the first time in certain adults and children with type 1 diabetes - the criteria are copied below and center on patients with lots of hypoglycemia. Unexpectedly, they are not just restricted to those experiencing lots of severe events. Indeed, adults could qualify for CGM if they have more than two episodes/week of asymptomatic hypoglycemia (we take that to mean "mild" hypoglycemia), hypoglycemia unawareness, or even extreme fear of hypoglycemia. That covers a meaningful number of patients in our view.

In children, the criteria are fairly similar (though less prescriptive) - CGM should be offered to those with frequent severe hypoglycemia, impaired hypoglycemia awareness associated with adverse consequences (e.g., seizures, anxiety), or inability to recognize/communicate about of hypoglycemia.

NICE has some important caveats: patients must be willing to commit to using CGM at least 70% of the time, and CGM should only be continued if A1c can be sustained at or below 7%, and/or there has been a reduction in A1c of 2.5% or more. These seem reasonable, though it is easy to imagine a patient being stripped of CGM with an A1c of 7.2%. How strict will it be?

The new CGM criteria could clearly be broader, but they are better than we might expect for the hardcore NICE, who is implicitly acknowledging that CGM is a cost-effective investment for certain patients. It's about time! We hope the new guidance will meaningfully expand CGM uptake in the UK, where it has historically been available only to those with special consideration from the National Health Service (NHS), or by paying out of pocket. Major credit goes to JDRF and JDRF UK, who participated in the process and are pleased with the results (even if they could be more positive). The news could also be a positive as the field looks to even stronger clinical evidence with closed-loop systems, particularly for avoiding nocturnal severe hypoglycemia.

In related news, NICE also released a new draft evaluation document in July on sensor augmented pumps (SAP), which reviews the Medtronic Veo and Animas Vibe. The assessment recommends that the Veo be covered for individuals with frequent and unpredictable episodes of severe hypoglycemia, or who feel significant anxiety about these episodes. NICE openly does not recommend the Animas Vibe, citing lack of evidence supporting sensor-augmented pumps without low glucose suspend. Even still, we see the Veo ruling as a positive step for future coverage of artificial pancreas systems, given the higher potential for

reducing hypoglycemia (with predictive suspend) and potentially improving A1c (with hybrid closed loop and beyond).

- **Underlying NICE's SAP decision is the cost of the Animas Vibe in the UK (more expensive than CSII + standalone CGM) and no evidence that it is more effective than CSII + standalone CGM.** From NICE's perspective, the Vibe costs more without any additional benefit, which makes it not cost effective.
    - **Beyond just price, we also wonder about the incremental benefit of standalone CGM vs. a sensor-augmented pump** - is the CGM component driving most of the clinical benefit? Recent T1D Exchange data (observational) has suggested very little difference in A1c between CGM+MDI vs. CGM+Pump users: 7.9% vs. 7.8% (<13 years), 8.0% vs. 8.1% (13-26 years), and 7.2% vs. 7.2% (>26 years). Of course, A1c is a pretty blunt metric to measure the impact of these two technologies, since they also impact hypoglycemia.
    - **Dexcom's DIaMonD study should help to answer this question.** As a reminder, the 338-patient, 20-center study aims to understand CGM outcomes in patients new to CGM. It appears that in the first phase, MDI patients will be randomized to either SMBG alone or CGM+SMBG. In phase 2, all users will move to CGM and be further randomized to add the Insulet OmniPod or stay on MDI. A great design in our view that overcomes a major criticism of the STAR-3 trial - as a reminder, the pump + CGM vs. MDI + SMBG design made it hard to tease out the individual contribution of CGM vs. pump. The inclusion criteria are quite broad (type 1 or type 2, no A1c requirement), and the estimated study completion date is still March 2016.
- **NICE's sensor-augmented pump (SAP) draft document goes through the clinical evidence ("weak") and cost-effectiveness modeling for the Veo and Vibe in detail,** and from much the wording, it's actually a major victory that the Veo will be covered. ASPIRE in-home was a critical study in this regard, but there are many statements in the report to the effect of "not cost-effective." We were glad to see NICE take into account fear of hypoglycemia, the short-term advantage of reducing severe hypoglycemia (vs. only focusing on A1c), and views from clinical experts. Still, the document makes it clear - as expected - that technologies are not going to get a free ride. Companies need to show the value of their devices on outcomes that matter.
    - **As part of the new draft SAP recommendations, NICE is asking Medtronic to collect, analyze, and publish data on the real-world impact of the Veo.** Much of this data is of course available through CareLink - frequency and duration of hypoglycemic events, time spent in hypoglycemia, number and duration of low glucose suspend events. It seems like Medtronic has done a lot of this already, though perhaps not enough to satisfy NICE.
    - **It is worth noting that the Veo has been available since 2010, meaning this took five years (!) to come through.** Clearly, there is a serious lag in decisions on this front, would could prevent UK patients from accessing artificial pancreas systems for some time.
- **NICE has retained its 2008 guidance on pumps**, which has limited uptake to patients with disabling hypoglycemia on MDI or those with an A1c >8.5% on MDI despite a high level of care. Following initiation, pumps will only be continued if there is a sustained improvement in glycemic control (fall in A1c), or a sustained decrease in the rate of hypoglycemic episodes (magnitude unspecified).
- **NICE does not provide explicit definitions for severe hypoglycemia in their guidance, but seems to define it broadly in patient-focused material:** "Most people with type 1 diabetes have hypos (hypoglycemia - low blood sugar levels) quite often. *Most hypos are mild, but some can be severe, which means that that you need help from someone else to treat the hypo. The*

fewer hypos you have, the better." Encouragingly, this definition of hypoglycemia (i.e., need for third party assistance) is a lower bar than the more stringent seizure/loss of consciousness definition.

Close Concerns Questions

- How will the new policy affect CGM uptake in the UK? What fraction of UK patients are on CGM now, either through appeals or paying out of pocket?
- Will Abbott's FreeStyle Libre fall under CGM criteria? How will the company's ongoing reimbursement studies affect coverage, if at all?
- Will NICE reconsider its draft decision not to cover the Vibe once it finalizes the SAP evaluation?
- Will the MiniMed 640G and 670G be reimbursed with wider criteria? How long will it take NICE to evaluate these devices?
- Could Bluetooth-enabled CGM (e.g., Dexcom's G5, Guardian Mobile) emerge as more cost effective, given potentially lower cost (no need for a receiver) and higher potential clinical impact (better data, higher utilization, more convenience)?
- What level of efficacy (on hypoglycemia or A1c) will NICE want to see to cover automated insulin delivery?

NICE on CGM in Adults

Pages 23-24 here.

- 1.6.21 Do not offer real-time continuous glucose monitoring routinely to adults with type 1 diabetes. [new 2015]
- 1.6.22 Consider real-time continuous glucose monitoring for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimized use of insulin therapy and conventional blood glucose monitoring:
    - More than 1 episode a year of severe hypoglycemia with no obviously preventable precipitating cause.
    - Complete loss of awareness of hypoglycemia.
    - Frequent (more than 2 episodes a week) asymptomatic hypoglycemia that is causing problems with daily activities.
    - Extreme fear of hypoglycemia.
    - Hyperglycemia (HbA1c level of 75 mmol/mol [9%] or higher) that persists despite testing at least 10 times a day (see recommendations 1.6.11 and 1.6.12).
    - Continue real-time continuous glucose monitoring only if HbA1c can be sustained at or below 53 mmol/mol (7%) and/or there has been a fall in HbA1c of 27 mmol/mol (2.5%) or more. [new 2015]
- 1.6.23 For adults with type 1 diabetes who are having real-time continuous glucose monitoring, use the principles of flexible insulin therapy with either a multiple daily injection insulin regimen or continuous subcutaneous insulin infusion (CSII or insulin pump) therapy. [new 2015]
- 1.6.24 Real-time continuous glucose monitoring should be provided by a centre with expertise in its use, as part of strategies to optimise a person's HbA1c levels and reduce the frequency of hypoglycemic episodes. [new 2015]

NICE on CGM in Children and Young People

Pages 21-22 here.

- 1.2.62 Offer ongoing real-time continuous glucose monitoring with alarms to children and young people with type 1 diabetes who have:
    - frequent severe hypoglycemia; or
    - impaired awareness of hypoglycemia associated with adverse consequences (for example, seizures or anxiety); or
    - inability to recognize, or communicate about, symptoms of hypoglycemia (for example, because of cognitive or neurological disabilities). [new 2015]
- 1.2.63 Consider ongoing real-time continuous glucose monitoring for:
    - neonates, infants and pre-school children
    - Children and young people who undertake high levels of physical activity (for example sport at a regional, national or international level)
    - children and young people who have comorbidities (for example anorexia nervosa) or who are receiving treatments (for example corticosteroids) that can make blood glucose control difficult. [new 2015]
- 1.2.64 Consider intermittent (real-time or retrospective) continuous glucose monitoring to help improve blood glucose control in children and young people who continue to have hyperglycemia despite insulin adjustment and additional support. [new 2015]

-- by Adam Brown, Ava Runge, and Kelly Close