**Clinical Scenario:** 57 yo male with PMHx of DM 2 and CAD on oral medications with Ha1c > 8.0 despite exercise and moderate dietary modifications. He is asking about insulin regimens as he would like to take as few injections as possible.

**Clinical Question:** What is the efficacy of various insulin regimens after failure of oral therapy alone based on ability to reduce Ha1c <7% and have fewest complications?

**Search Method:** Used PubMed and ADA website.
- MeSH terms: DM type 2, insulin, efficacy
- Combined with: Ha1c

**Article:** Giugliano, Maiorino, Bellastella, Chiodini and Esposito; Treatment Regimens with Insulin Analogues and Haemoglobin A1c Target of <7% in Type 2 Diabetes: A systematic review; *Diabetes Research and Clinical Practice; Vol 92, Pages 1-10: 2011.*

**A Quick Summary**

**Background:** Systematic Review analyzing 4 various insulin regimens including prandial, biphasic, basal and basal-bolus to determine the most effective therapy for reducing Ha1c levels < 7%. Secondary outcomes of hypoglycemic episodes, weight gain and insulin dose were also evaluated.

**Objectives:**
- determine efficacy of various insulin regimens after failure of oral therapy only to reduce Ha1c < 7% to prevent cardiovascular complications
- determine safety of various regimens in regards to hypoglycemic episodes and wt gain

**Methods:**

**Patient data:**
- Population: individuals enrolled in randomized control trials with the following exclusion criteria:
  - Age > 18, diagnosis of DM 2.
  - Systematic Review: Studies that were randomized controlled trials, at least 3mo follow up, or if study population < 30.
  - Inclusion: >18 yo, Dx of DM 2,
  - Exclusion: studies < 30 participants, < 3mo follow up
  - Outcome: Primary: Ha1c reduction < 7%, Secondary: wt gain and hypoglycemic episodes
  - 48 trials, 85 arms with 30,588 patients
  - Databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and CINAHL; publication dates 2000-2010

**Statistical analysis:**
- Systematic Review and meta-analysis of previously described RCTs based on exclusion/inclusion criteria (2000-2010)
- Heterogeneity across studies for each regimen assessed by Q² statistics

**Results:**

<table>
<thead>
<tr>
<th></th>
<th>Ha1c &lt; 7%</th>
<th>Wt gain</th>
<th>Hypo Episodes (mean/patient/30 days)</th>
<th>Insulin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>41.4%</td>
<td>1.75kg</td>
<td>0.5</td>
<td>0.48 U/kg</td>
</tr>
<tr>
<td>N = 17588</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biphasic</td>
<td>46.5%</td>
<td>3kg</td>
<td>0.37</td>
<td>0.62 U/kg</td>
</tr>
<tr>
<td>N = 9237</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prandial</td>
<td>39.6%</td>
<td>2.3kg</td>
<td>0.67</td>
<td>0.5 U/kg</td>
</tr>
<tr>
<td>N = 1605</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal-Bolus</td>
<td>53.9%</td>
<td>2.75kg</td>
<td>0.88</td>
<td>0.89 U/kg</td>
</tr>
<tr>
<td>n = 2114</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical Appraisal Tool

Are the Results Valid?
- Was the sample of patients representative? Yes.
- Were the patients sufficiently homogenous with respect to the prognostic risk? Yes.
- Was the follow-up sufficiently complete? Yes and No. The study was designed to evaluate efficacy of reduction in Ha1c and did exclude any studies with < 3mo follow up. It does discuss the limitations for long term outcomes as only 1 study had long term follow up of 963 days.
- Were objective and unbiased outcome criteria used? Yes, however double blind studies were not available due to nature of the study and safety with double blinding and insulin usage.

What Are the Results?
- How likely are the outcomes over time? Would expect general reproducibility based on controlled clinical factors for future studies.
- How precise are the estimates of likelihood? Reasonable – there was much heterogeneity across the different studies in each regimen group. Systematic review limited by the methods and controls in each study. In regards to insulin use numerous factor can be involved which would be hard to control such as diet and exercise adherence.

How Can I Apply the Results to Patient Care?
- Were the study patients and their management similar to those in my practice? Yes.
- Was the follow-up sufficiently long? Long enough to make general determination of best regimen for your patient at that time however long term effects were not evaluated. However, other studies have shown improved CV outcomes with improved glycemic control so one may be able to extrapolate this regimen review with long term outcomes.
- Can I use the results in the management of patients in my practice? Yes, I could take this data and utilize the best option for the patients control of DM 2 based on adherence, complexity, wt gain and efficacy.

Conclusion: The systematic review was designed to evaluate various insulin regimens (basal, parandial, biphasic and basal-bolus) and their efficacy in reducing Ha1c < 7%. The review had good exclusion criteria as well as population numbers. However, it did have large variability between the studies in each regimen group. Most of the studies included oral regimens as well as insulin therapy but did not address dosing for these medications.

Overall, it appears that of the 4 insulin regimens, basal-bolus QID injections are the most effective at reducing Ha1c levels at a consequence of increased complexity, increase wt gain and more hypoglycemic episodes. Continuing oral therapy after initiation of insulin appears to be more effective than insulin alone. Overall, tailoring the DM regimen that you as the primary provider feel the patient would have the most adherence and least complications would be beneficial (i.e. simple regimens with fewer hypoglycemic episodes for elderly at greater risk for severe problems vs more complex therapy for younger individuals that are motivated to monitor their sugars and respond appropriately to hypoglycemic episodes.).

Any questions?