The changing landscape of T2DM management: balancing new options for glycemic control & outcomes

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Seoul 5 November, 2016
Diabetes Treatment

Why?

1. Metabolic control
2. Microvascular complications
3. Macrovascular complications
4. Overall survival
5. Quality of life
Diabetes Treatment

Why?

1. Metabolic control
2. Microvascular complications
3. Macrovascular complications
4. Overall survival
5. Quality of life
Diabetologist’s Issues

- Patient-centered approach
- Early treatment
- Combination treatment
- Compliance
- Therapeutic response
Diabetologist’s Issues

- Patient-centered approach
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- Combination treatment
- Compliance
- Therapeutic response
Heterogeneity re. comorbidities

- Obesity
- Hypertension
- Diabetes
Heterogeneity of Type 2 Diabetes

- Autoimmune (LADA) & genetic background
- Age of onset (the elderly)
- Duration (β-cell loss)
- Ethnicity
- Obesity
- Circumstances (pregnancy, trauma, infections, HCV, etc.)
- Previous treatments (steroids, neuroleptics, etc.)
- Severity of presentation
- Microvascular complications
- Macrovascular disease
Heterogeneity of type 2 diabetes

Pre-DM → T2D → Complications

Progression → Response to Treatment

Presentation → Development
Healthy eating, weight control, increased physical activity, and diabetes education

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>high</td>
</tr>
<tr>
<td>Efficacy*</td>
<td>low risk</td>
</tr>
<tr>
<td>Hypo risk</td>
<td>neutral / loss</td>
</tr>
<tr>
<td>Weight</td>
<td>GI / lactic acidosis</td>
</tr>
<tr>
<td>Side effects</td>
<td>low</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>Thiazolidinedione</td>
</tr>
<tr>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>Efficacy*</td>
<td>moderate risk</td>
</tr>
<tr>
<td>Hypo risk</td>
<td>low risk</td>
</tr>
<tr>
<td>Weight</td>
<td>gain</td>
</tr>
<tr>
<td>Side effects</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td>Costs*</td>
<td>low</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea + TZD</td>
<td>Sulfonylurea + DPP-4-i</td>
</tr>
<tr>
<td>or SGLT2-i</td>
<td>or GLP-1-RA</td>
</tr>
<tr>
<td>or GLP-1-RA</td>
<td>or Insulin</td>
</tr>
<tr>
<td>or Insulin</td>
<td>or DPP-4-i</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:

<table>
<thead>
<tr>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal insulin +</td>
</tr>
</tbody>
</table>
Diabetologist’s Issues

- Patient-centered approach
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Brief Insulin Course in New Diabetes

Absolute Risk Reduction (ARR)

How early is early?

**UKPDS**: Newly-diagnosed T2D, intensive vs conventional Tx:
  Diabetes-related mortality after 30 yrs
  RRR = 17%; ARR = 2.5%; NNT = 40

**ORIGIN**: Recent T2D, insulin vs SoC: neutral on CVD

**DCCT/EDIC**: 1-5-yr duration T1D, 7-yr intensive vs conventional Tx:
  Total mortality at 27 yrs
  RRR = 33%; ARR = 2.7%; NNT = 37
Diabetologist’s Issues

- Patient-centered approach
- Early treatment
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Timeline of the Introduction of Treatment Options for Type 2 Diabetes

- Animal insulin
- Sulfonylureas
- Metformin
- Thiazolidinediones
- Long Acting Insulin Analogs
- Glinides
- Rapid Acting Insulin Analogs
- Human insulin
- Inhaled insulin
- GLP-1 Receptor Agonists
- Pramlintide
- Aspart
- DPP-4 Inhibitors
- SGLT2i

- 1922
- 1950s
- 1982-5
- 1995
- 1996
- 2001
- 2003
- 2005
- 2006
- 2007
- 2015
## Combination therapy

<table>
<thead>
<tr>
<th>Treatments</th>
<th>n = 7</th>
<th>n = 13</th>
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</thead>
<tbody>
<tr>
<td>Doublets</td>
<td>21</td>
<td>78</td>
</tr>
<tr>
<td>Triplets</td>
<td>35</td>
<td>286</td>
</tr>
<tr>
<td>Quadruplets</td>
<td>35</td>
<td>715</td>
</tr>
</tbody>
</table>
Rational combinations

Insulin +
- SGLT2 inhibitors
- GLP1-RA

*to reduce hypoglycaemia and curb weight gain*

or

SGLT2 inhibitors + GLP1-RA

*to enhance weight loss and blood pressure lowering*
Diabetologist’s Issues

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Secondary metformin failure

Compliance

![Graph showing compliance over weeks for different treatment regimens.](image)

<table>
<thead>
<tr>
<th>Study period</th>
<th>Study groupa</th>
<th>n</th>
<th>Persistence (in days)b</th>
<th>SD</th>
<th>Persistence rate (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year (360 days)</td>
<td>Metformin (M)</td>
<td>4033</td>
<td>183.8</td>
<td>142.7</td>
<td>51.06</td>
</tr>
<tr>
<td></td>
<td>Sulfonylurea (S)</td>
<td>11324</td>
<td>183.1</td>
<td>141.8</td>
<td>50.86</td>
</tr>
<tr>
<td></td>
<td>M + S</td>
<td>661</td>
<td>111.1</td>
<td>117.4</td>
<td>30.86</td>
</tr>
<tr>
<td>2 years (720 days)</td>
<td>Metformin</td>
<td>915</td>
<td>296.7</td>
<td>285.1</td>
<td>41.21</td>
</tr>
<tr>
<td></td>
<td>Sulfonylurea</td>
<td>2983</td>
<td>274.3</td>
<td>276.5</td>
<td>38.10</td>
</tr>
<tr>
<td></td>
<td>M + S</td>
<td>158</td>
<td>121.9</td>
<td>186.9</td>
<td>16.93</td>
</tr>
</tbody>
</table>

Factors Related to Nonadherence in Patients With Type 2 Diabetes

Only 23% of patients who had side effects reported the problems to their primary care physician.

*Number of prescribed medications, patient characteristics

N=128 patients with Type 2 Diabetes.

Diabetologist’s Issues

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- Therapeutic response
Therapeutic response: metrics

What response?

1. Fasting plasma glucose
2. Random plasma glucose
3. HbA$_{1c}$
4. Body weight
5. Hypoglycaemic episodes
Therapeutic response: metrics

How much response?

1. Fasting plasma glucose decrease ≥1.5 mmol/L
2. Fasting plasma glucose ≤7.0 mmol/L
3. Random plasma glucose ≤11.1 mmol/L
4. HbA1c decrease ≥0.5%
5. Body weight decrease ≥5%
6. Hypo: ≤1 severe episode/year
Therapeutic response: metrics

When?

1. Six months
2. One year
3. Three years
4. Five years
Therapeutic response: metrics

What response?

1. Fasting plasma glucose
2. Random plasma glucose
3. $\text{HbA}_{1c}$ + Body weight + Hypo’s
4. Body weight
5. Hypoglycaemic episodes
Relationship between baseline HbA$_1$c and treatment-induced changes in HbA$_1$c

Figure 2. Meta-Analysis of 67 Clinical Trials

Non-responders: primary

1. Pharmacokinetics
2. Suboptimal dose
3. Genetics
4. Tachyphylaxis
Non-responders: secondary

1. Disease progression
2. β-cell exhaustion
3. Weight gain
4. Acute medical/surgical events
   (= stress hyperglycaemia)
Identifying Responders and Non-responders

- Baseline HbA$_{1c}$ is predictive of a good HbA$_{1c}$ decrease
  - but not specific: a high HbA$_{1c}$ is a predictor of response for all anti-diabetic agents,
  - and a better relative response does not translate into more *achievers*. 
Identifying Responders and Non-responders

- **Baseline HbA\(_1c\)**: Yes, but not specific and not helpful in clinical practice

- **Age**
- **Duration of Diabetes**
- **Gender**
- **Body weight at baseline**
- **\(\beta\)-cell function**
- **Genetics**
- **Endogenous GLP1 secretion**
- **Endogenous DPP4 activity**
- **Pharmacokinetics**

**No predicting value**, at least for clinical use
Therapeutic response: problems

For whom?

1. Physician’s satisfaction
2. Patient’s satisfaction
3. Healthcare system compliance
There is no consensus to define the bad responders (or the good), on an individual basis, within this continuum of decrease

The most commonly used criterium is «the achievers»

The number of patients reaching the ADA/EASD HbA\textsubscript{1c} target of 7% are considered as target achievers in clinical studies.
Diabetologist’s Expectations

- Better patient-specialist-primary care relation
- Earlier combination treatment based on drug mode of action
- Targeted CVD outcome trials in special populations
- Prevention: screening, deep phenotyping, and treatment of high-risk subjects