Initiating Treatment for Type 2 Diabetes: One Drug at a Time

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All honoraria directed toward a non-profit which supports education and research
Metformin remains the optimal drug for monotherapy. Its low cost, proven safety record, weight neutrality and possible benefits on cardiovascular outcomes have secured its place as the favored initial drug choice.

"Initial combination therapy with metformin plus a second agent may allow patients to achieve HbA1c targets more quickly than sequential therapy.

"A reasonable threshold HbA1c for this consideration is ≥ 9%.
ADA/EASD Position Statement: Managing Hyperglycemia in Type 2 Diabetes

“Of course, there is no proven overall advantage to achieving a glycemic target more quickly by a matter of weeks or even months. Accordingly, as long as close patient follow-up can be ensured, prompt sequential therapy is a reasonable alternative.

Garber et al. Endocrine Practice 22:1, 2016
AACE Consensus Statement

“Combination therapy is usually required and should involve agents with complementary mechanisms of action

“Patients who present with an A1c of > 7.5% should be started on metformin plus another agent in addition to lifestyle therapy

Garber et al. Endocrine Practice 22:1, 2016

So, Where’s the Controversy?

<table>
<thead>
<tr>
<th>6.0</th>
<th>6.5</th>
<th>7.0</th>
<th>7.5</th>
<th>8.0</th>
<th>8.5</th>
<th>9.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>Monotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</table>
Arguments for Combination Therapy

- Multiple metabolic abnormalities contribute to hyperglycemia in T2DM
- The efficacy of any single agent is limited – combination therapy is necessary to get patients to goal
- Combinations of drugs with complementary mechanisms of action will be significantly better
- Getting to goal faster will improve outcomes

Multiple Metabolic Defects Contribute to Hyperglycemia in T2DM

Islet β-cell
- Impaired Insulin Secretion
- Decreased Glucose Uptake
- Decreased Incretin Effect
- Increased HGP
- Decreased Glucose Reabsorption

Islet α-cell
- Increased Glucagon Secretion
- Increased Glucose Reabsorption
- Increased Lipolysis
- Increased Glucose Uptake
- Neurotransmitter Dysfunction

From DeFronzo, Diabetes: 2009
12 Classes of Antihyperglycemic Agents for T2DM

<table>
<thead>
<tr>
<th>Class</th>
<th>Δ_A1c</th>
<th>Hypoglycemia</th>
<th>Weight Change</th>
<th>Dosing</th>
<th>Other Safety Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1.5</td>
<td>No</td>
<td>Neutral</td>
<td>2</td>
<td>GI, lactic acidosis, B12 deficiency</td>
</tr>
<tr>
<td>Basal insulin analog</td>
<td>1.5–2.5</td>
<td>Yes</td>
<td>Gain</td>
<td>1, injected</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Rapid-acting insulin</td>
<td>1.5–2.5</td>
<td>Yes</td>
<td>Gain</td>
<td>1-4, injected</td>
<td></td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1.5</td>
<td>Yes</td>
<td>Gain</td>
<td>1</td>
<td>Allergies, secondary failure</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>0.5–1.4</td>
<td>No</td>
<td>Gain</td>
<td>1</td>
<td>Edema, CHF, bone fractures</td>
</tr>
<tr>
<td>Short-acting GLP-1 RAs</td>
<td>0.5–1.0</td>
<td>No</td>
<td>Loss</td>
<td>2, injected</td>
<td>GI, ?, pancreatitis, ARF</td>
</tr>
<tr>
<td>Long-acting GLP-1 RAs</td>
<td>&lt;1.5</td>
<td>No</td>
<td>Loss</td>
<td>1, injected</td>
<td>GI, ?, pancreatitis, ?,MTC, ?,ARF</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>1–1.5</td>
<td>Yes</td>
<td>Gain</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Nateglinide</td>
<td>0.5–0.8</td>
<td>Rare</td>
<td>Gain</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>0.5–0.8</td>
<td>No</td>
<td>Neutral</td>
<td>3</td>
<td>GI</td>
</tr>
<tr>
<td>Amylin mimetics</td>
<td>0.5–1.0</td>
<td>No</td>
<td>Loss</td>
<td>3, injected</td>
<td>GI</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>0.6–0.8</td>
<td>No</td>
<td>Neutral</td>
<td>1</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Bile acid sequestant</td>
<td>0.5</td>
<td>No</td>
<td>Neutral</td>
<td>1 or 2</td>
<td>GI</td>
</tr>
<tr>
<td>Bromocriptine quick release</td>
<td>0.7</td>
<td>No</td>
<td>Neutral</td>
<td>1</td>
<td>GI</td>
</tr>
<tr>
<td>SGLT2s</td>
<td>0.8–1.0</td>
<td>No</td>
<td>Loss</td>
<td>1</td>
<td>Genital mycotic infections</td>
</tr>
</tbody>
</table>

G1 = gastrointestinal; GLP-1 = glucagon-like peptide-1; RA = receptor agonist; CHF = congestive heart failure; ARF = acute renal failure; MTC = medullary thyroid carcinoma; DPP-4 = dipeptidyl peptidase-4; SGLT2 = sodium-dependent glucose cotransporter-2.


Complementary Mechanisms of Action of Current Diabetes Medications

From DeFronzo, Diabetes: 2009

Insulin
Sulfonylureas
Meglitinides

GLP-1 RA
DPP-4 inhibitors

Increased
Incretin Effect

Increased
Lipolysis

Increased Glucose
Reabsorption

Decreased
Glucose
Uptake

TZDs

SGLT-2
inhibitors

From DeFronzo, Diabetes: 2009
Possible SUs and GLNs include glimepiride, glipizide, glyburide, nateglinide, and repaglinide; Possible TZDs include pioglitazone and rosiglitazone; Possible DPP-4 inhibitors include alogliptin, sitagliptin, linagliptin, and saxagliptin; Possible SGLT-2 inhibitors include canagliflozin, dapagliflozin, and empagliflozin; Possible GLP-1 RAs include exenatide twice daily, exenatide once weekly, liraglutide, dulaglutide, and albiglutide; Possible metformin drugs include standard and extended release formulations.

**Potential 2-Drug Noninsulin Combinations in the US**

<table>
<thead>
<tr>
<th>SU/GLN&lt;sup&gt;a&lt;/sup&gt; (5 Agents)</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>TZD&lt;sup&gt;b&lt;/sup&gt; (2 Agents)</td>
<td>4</td>
</tr>
</tbody>
</table>

159 Possible Noninsulin Combinations in 2-Drug Regimens

**Which is best?**

(What about bromocriptine and colesevelam?)

*Possible SUs and GLNs include glimepiride, glipizide, glyburide, nateglinide, and repaglinide; Possible TZDs include pioglitazone and rosiglitazone; Possible DPP-4 inhibitors include alogliptin, sitagliptin, linagliptin, and saxagliptin; Possible SGLT-2 inhibitors include canagliflozin, dapagliflozin, and empagliflozin; Possible GLP-1 RAs include exenatide twice daily, exenatide once weekly, liraglutide, dulaglutide, and albiglutide; Possible metformin drugs include standard and extended release formulations.*

**Glycemic Efficacy of Initial Combination Therapy With Sitagliptin + Metformin**

24-Week Placebo-Adjusted Results

Mean A1C = 8.8%

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change From Baseline, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin 100 mg qd</td>
<td>-1.0</td>
</tr>
<tr>
<td>Metformin 500 mg bid</td>
<td>-1.6</td>
</tr>
<tr>
<td>Metformin 1,000 mg bid</td>
<td>-2.1</td>
</tr>
<tr>
<td>Sitagliptin 50 mg +</td>
<td></td>
</tr>
<tr>
<td>Metformin 500 mg bid</td>
<td></td>
</tr>
<tr>
<td>Sitagliptin 50 mg +</td>
<td></td>
</tr>
<tr>
<td>Metformin 1,000 mg bid</td>
<td></td>
</tr>
</tbody>
</table>

<sup>*LSM change from baseline without adjustment for placebo.*</sup>

qd=once a day; bid=twice a day.

**Dapagliflozin 10 mg vs. Metformin XR vs. Combination Therapy: A1C at Week 24**

- **N**
  - Dapa 10 mg: 216
  - MET XR 2,000 mg: 203
  - Dapa 10 mg + MET XR: 202

- **BL mean (%)**
  - Dapa 10 mg: 9.03
  - MET XR 2,000 mg: 9.03
  - Combination: 9.10

- **Study week**
  - BL
  - 4
  - 8
  - 12
  - 16
  - 20
  - 24

- **Δ A1C (%) with 95% CI**

  - Dapa 10 mg vs. MET XR: -0.01 (-0.22, 0.20)
  - Combination vs. monotherapies: -1.44 (-0.53, -0.54)

*P < 0.0001 vs monotherapy*


**Initial Combination Therapy: Alogliptin + Pioglitazone**

- **A1c <9.0%**
  - Alogliptin 25 mg: -0.77
  - ACTOS 30 mg: -1
  - 12.5 + 30 mg: -1.33
  - 25 + 30 mg: -1.3

- **A1c >=9.0%**
  - Alogliptin 25 mg: -1.2
  - ACTOS 30 mg: -1.38
  - 12.5 + 30 mg: -1.91

***p-value <0.001 when compared to ACTOS 30 mg***

***p-value <0.001 when compared to Alogliptin 25 mg***
Initial Combination Therapy with Empagliflozin and Linagliptin

N=674 individuals with T2DM who had not received diabetes therapy for ≥12 weeks (week 24 data).


<table>
<thead>
<tr>
<th>Change From Baseline in A1c, %</th>
<th>Mean Baseline</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.99% (n=134)</td>
<td>-0.21</td>
<td>0.001</td>
</tr>
<tr>
<td>8.04% (n=135)</td>
<td>-0.21</td>
<td>0.001</td>
</tr>
<tr>
<td>7.99% (n=133)</td>
<td>-0.21</td>
<td>0.001</td>
</tr>
<tr>
<td>8.05% (n=132)</td>
<td>-0.21</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change From Baseline in Body Weight, kg</th>
<th>Mean Baseline</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.14 (-0.33, 0.06)</td>
<td>0.179</td>
<td>0.001</td>
</tr>
<tr>
<td>0.41 (-0.61, -0.21)</td>
<td>0.362</td>
<td>0.001</td>
</tr>
<tr>
<td>0.57 (-0.76, -0.21)</td>
<td>-0.001</td>
<td></td>
</tr>
</tbody>
</table>

Empagliflozin 25 mg/Linagliptin 5 mg
Empagliflozin 10 mg/Linagliptin 5 mg
Empagliflozin 25 mg
Empagliflozin 10 mg
Linagliptin 5 mg


ENDURE Study design

Run-in

<table>
<thead>
<tr>
<th>Screening</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin + ALO 12.5mg</td>
<td></td>
</tr>
<tr>
<td>Metformin + ALO 25mg</td>
<td></td>
</tr>
<tr>
<td>Metformin + Glipizide 5mg to 20mg</td>
<td></td>
</tr>
</tbody>
</table>

N=2639

4 Weeks 104 Weeks

Mean glipizide dose at end of study: 5.2mg

**ENDURE: Change in A1c after 104 Weeks with Alo/Met vs Glip/Met**

<table>
<thead>
<tr>
<th>Week 52 (interim analysis n=1,588)</th>
<th>Week 104 (n=1,089)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c ≤6.5%</td>
<td>HbA1c ≤7.0%</td>
</tr>
<tr>
<td>Subjects achieving target HbA1c at Week 104 (%)</td>
<td></td>
</tr>
<tr>
<td>Change from baseline in FPG (mg/dL)</td>
<td></td>
</tr>
</tbody>
</table>

*Non-inferiority to MET + glipizide #Superiority to MET + glipizide (P=0.019)


**Arguments for Combination Therapy**

- Multiple metabolic abnormalities contribute to hyperglycemia in T2DM
  - True

- The efficacy of any single agent is limited – combination therapy is necessary to get patients to goal
  - One drug is often enough

- Combinations of drugs with complementary mechanisms of action will be significantly better
  - Meh....

- Getting to goal faster will improve outcomes
  - Where’s the evidence?
Arguments Against Initial Combination Therapy

- One drug is often sufficient for those with an A1c 7.5-9
- There is a lack of evidence that early control improves outcomes or durability of response
- There is virtually no comparative efficacy data on initial combination therapies
- Decreased flexibility of dosing with initial combination – diminished opportunity to personalize therapy
- Attribution of side effects may be confounded

Arguments Against Initial Combination Therapy

- Pill burden may decrease adherence
- Costs are higher
- Insurance companies only cover stepped-care
- Polypharmacy may contribute to adverse events
UKPDS: Diet Run-in in New Onset T2DM

Adherence Decreases With Increasing Frequency of Dosing


Polypharmacy increases the number of adverse drug events for those with T2DM including:

- Severe hypoglycemia
- Drug-drug interactions
- Interactions with coexisting comorbidities

The higher the number of medications, the less likely the patient will remain adherent with the treatment regimen.


Annual Total Expenditures for Diabetes Per Person 2014 (USD)

Source: IDF Diabetes Atlas 2015
**Field Research**

Metformin is cheaper than dirt

**Lowest Available Retail Price of Diabetes Drugs in United States – 2015**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Price for 1-mo Supply</th>
<th>Retailer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1000 mg BID</td>
<td>$0</td>
<td>Publix</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>4 mg QD</td>
<td>$8</td>
<td>Walmart</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>30 mg QD</td>
<td>$14.50</td>
<td>Walmart</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>100 mg QD</td>
<td>$343.37</td>
<td>Publix</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>5 mg QD</td>
<td>$343.38</td>
<td>Publix</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>300 mg QD</td>
<td>$355.72</td>
<td>Publix</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>5 mg QD</td>
<td>$334.59</td>
<td>Publix</td>
</tr>
<tr>
<td>Exenatide</td>
<td>10 mcg BID</td>
<td>$456.09</td>
<td>Walmart</td>
</tr>
<tr>
<td>Exenatide QW</td>
<td>2 mg QW</td>
<td>$489.92</td>
<td>Publix</td>
</tr>
</tbody>
</table>

Source: GoodRx - Downloaded 2015
Physicians Delay Intensifying Therapy for Months – This is the Real Problem!

Summary

- Sequential therapy is appropriate for patients with an A1c < 9%. It works!
- Sequential therapy allows for better personalization of therapy, minimizes side effects and contains costs
- Early control does not improve outcomes for patients
- There is a lack of clinical trial evidence to guide initial combination therapy
- Clinical inertia must be avoided