Treating Earlier and Effectively with Combination Therapies
Aim

Provide practical guidance on improving diabetes care through highlighting the need for:

• a sense of urgency in treating to target

• earlier introduction of combination therapy

• consideration of patient profile

• use of combinations of drugs with complementary mechanisms of action
Need for an early and intensive approach to type 2 diabetes management

- At diagnosis of type 2 diabetes:
  - 50% of patients already have complications\(^1\)
  - up to 50% of β-cell function has already been lost\(^2\)

- Current management:
  - two-thirds of patients do not achieve target HbA\(_{1c}\)\(^3,4\)
  - majority require polypharmacy to meet glycemic goals over time\(^5\)
Barriers to achieving good glycemic control

- Limitations of reactive, stepwise treatment
- Therapy not matched to the individual
- Conservative prescribing of antidiabetic agents
Limitations of reactive, stepwise treatment
Conservative management of glycemia: traditional stepwise approach

- Diet and exercise
- OAD* monotherapy
- OAD monotherapy up-titration
- OAD combination
- OAD + basal insulin
- OAD + multiple daily insulin injections

HbA\(_{1c}\) = 6.5%
HbA\(_{1c}\) = 7%

OAD = oral antidiabetic

Drawbacks of the stepwise approach

- Even short periods of hyperglycemia increase risk of complications\(^1\)\(^–\)\(^3\)
- A proactive approach is required to get patients to achieve their glycemic goals sooner

![Graph showing incidence of complications vs. updated mean HbA\(_{1c}\) levels]

Diet and exercise are beneficial to good glycemic control

- Lifestyle changes can have beneficial outcomes\textsuperscript{1,2}
- Patients may require motivation to encourage them to follow a healthy diet and take exercise

\textsuperscript{2}Macauley KA, et al. Diabetes Care 2002; 25:442–452.
Benefits of diet and exercise may be difficult to maintain in the long term

- Stepwise treatment may lead to delays
- Pharmacological therapy should be introduced in tandem with lifestyle changes
Delays often occur between stepping up from monotherapy to combination therapy

Length of time between first monotherapy HbA$_{1c}$ > 8.0% and switch/addition in therapy (months)

- **Metformin only**: 14.5 months (n = 513)
- **Sulfonylurea only**: 20.5 months (n = 3394)

Up-titrating monotherapy to the maximum recommended dose may not provide benefit.

Proactive management of glycemia: early combination approach

Diet and exercise
OAD* monotherapy
OAD combinations
OAD up-titration
OAD + basal insulin
OAD + multiple daily insulin injections

HbA₁c (%)

Duration of diabetes

ACTION POINT:
HbA₁c = 7%
HbA₁c = 6.5%

*OAD = oral antidiabetic
Potential advantages of early combination therapy

• Earlier achievement of therapeutic goals
• Potential reduction in risk of side effects if you combine drugs at lower doses versus up-titration of single dose
• Opportunity to combine oral antidiabetic drugs with complementary modes of action
• Potential to delay disease progression
Benefits of adding TZD to sub-maximal sulfonylurea compared with up-titration

Patients achieving HbA$_1c$ $< 7\%$ (%)

- Up-titrated SU + PBO: 22%
- RSG + SU: 50%

Abbreviations: PBO, placebo; RSG, rosiglitazone; SU, sulfonylurea; TZD, thiazolidinediones.

Benefits of adding TZD to sub-maximal metformin compared with up-titration

HbA\textsubscript{1c}

- Patients achieving HbA\textsubscript{1c} < 7\% (%)
  - MET 1 g/day + MET 1 g/day: 48\%
  - MET 1 g/day + RSG 8 mg/day: 58\%

Gastrointestinal side effects

- Patients discontinuing due to GI disturbances (%)
  - MET 1 g/day + MET 1 g/day: 7\%
  - MET 1 g/day + RSG 8 mg/day: 3\%

Abbreviations: MET, metformin; RSG, rosiglitazone; TZD, thiazolidinediones.

Benefits of glyburide/metformin versus monotherapy as initial pharmacotherapy

Patients achieving HbA$_{1c}$ < 7%

<table>
<thead>
<tr>
<th></th>
<th>GLY</th>
<th>MET</th>
<th>GLY/MET</th>
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<tbody>
<tr>
<td>Patients</td>
<td>70</td>
<td>60</td>
<td>80</td>
</tr>
</tbody>
</table>

Abbreviations: GLY, glyburide; MET, metformin.

How quickly should patients be reaching $\text{HbA}_{1c}$ targets?

The Global Partnership recommends:

Treat patients intensively so as to achieve target $\text{HbA}_{1c} < 6.5\%$* within 6 months of diagnosis

*Or fasting/preprandial plasma glucose < 110 mg/dL (6.0 mmol/L) where assessment of $\text{HbA}_{1c}$ is not possible

When should combination therapy be introduced?

*The Global Partnership recommends:*

After 3 months, if patients are not at target HbA$_{1c}$ < 6.5%, consider combination therapy

*Or fasting/preprandial plasma glucose < 110 mg/dL (6.0 mmol/L) where assessment of HbA$_{1c}$ is not possible*
Therapy not matched to the individual
Individuals with high baseline HbA1c require more intensive treatment

- Risk of complications increases with HbA1c
- Individuals with high baseline values require particularly urgent and intensive treatment
- Monotherapy is often insufficient in these individuals and combination therapy should be initiated earlier

How should patients with high baseline HbA$_{1c}$ be managed?

*The Global Partnership recommends:*

Initiate combination therapy or insulin immediately for all patients with HbA$_{1c}$ ≥ 9% at diagnosis

Inappropriate prescribing of antidiabetic agents
Reasons for conservative prescribing patterns

- Familiarity with traditional agents
- Concerns regarding safety of newer agents
- Perceived lack of efficacy of antidiabetic agents
Treatment options for type 2 diabetes

- **Sulfonylureas**
  - 1st generation e.g. chlorpropamide, tolbutamide
  - 2nd generation e.g. glyburide, gliclazide, glipizide,agliquidone
  - 3rd generation e.g. glimepiride
  - Modified release

- **Glinides/meglitinides**
  - Non-sulfonylureic e.g. repaglinide
  - Amino acid derivatives e.g. nateglinide

- **Biguanides**
  - e.g. metformin

- **Thiazolidinediones**
  - e.g. rosiglitazone, pioglitazone

- **α-glucosidase inhibitors**
  - e.g. acarbose

- **Insulin**
  - regular
  - intermediate/long acting
  - pre-mixed
  - analogs
    - rapid acting
    - long acting

- **Fixed-dose oral antidiabetic drug combinations**
  - e.g. glyburide/metformin, glipizide/metformin, rosiglitazone/metformin
Choosing antidiabetic agents: efficacy

<table>
<thead>
<tr>
<th>EFFICACY</th>
<th>Insulin secretagogues</th>
<th>Metformin</th>
<th>α-glucosidase inhibitors</th>
<th>TZDs*</th>
<th>Insulin</th>
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<tbody>
<tr>
<td>Effect on FPG/HbA₁c</td>
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<td>Effect on plasma insulin</td>
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<td>Effect on insulin resistance</td>
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<td>Effect on insulin secretion</td>
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= reduced levels  

= increased levels  

= no significant effect

*TZDs = thiazolidinediones

Choosing antidiabetic agents: safety and tolerability

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<thead>
<tr>
<th>SAFETY AND TOLERABILITY</th>
<th>ANTIDIABETIC AGENTS</th>
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<tr>
<td></td>
<td>Insulin secretagogues</td>
</tr>
<tr>
<td>Risk of hypoglycemia¹,²</td>
<td>✓</td>
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<tr>
<td>Weight gain¹,²</td>
<td>✓</td>
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<tr>
<td>Gastrointestinal side effects¹</td>
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<td>Lactic acidosis¹</td>
<td>✓</td>
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<tr>
<td>Edema³</td>
<td>✓</td>
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= treatment-related adverse event  = not commonly seen in monotherapy


*TZDs = thiazolidinediones
Choosing oral antidiabetic agents: mechanism of action

- **α-glucosidase inhibitors**
  - ↓ Carbohydrate breakdown/absorption

- **Sulfonylureas/meglitinides**
  - ↑ Insulin secretion

- **Biguanides**
  - ↓ Glucose output
  - ↓ Insulin resistance

- **Thiazolidinediones**
  - ↓ Insulin resistance

What are the ideal components for combination therapy?

*The Global Partnership recommends:*

Use combinations of oral antidiabetic agents with complementary mechanisms of action

Paradigm for early combination treatment

If HbA$_{1c}$ $\geq$ 9% at diagnosis
Initiate combination therapy$^\dagger$ or insulin in parallel with diet/exercise

If HbA$_{1c}$ < 9% at diagnosis
Initiate monotherapy in parallel with diet/exercise

If HbA$_{1c}$ > 6.5%* at 3 months
Initiate combination therapy$^\dagger$ in parallel with diet/exercise

Treat to goal of HbA$_{1c}$ < 6.5%* by 6 months

*Or fasting/preprandial plasma glucose < 110 mg/dL (6.0 mmol/L) where assessment of HbA$_{1c}$ is not possible
$^\dagger$Combination therapy should include agents with complementary mechanisms of action