降血糖藥物之最新進展及常見問題

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Glycemic Management of Type 2 Diabetes Mellitus

Faramarz Ismail-Beigi, M.D., Ph.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

KEY CLINICAL POINTS

GLYCEMIC CONTROL IN TYPE 2 DIABETES MELLITUS

• Intensive glycemic control reduces the risk of microvascular complications of type 2 diabetes, but the effect of strict glycemic control on the risk of macrovascular disease (especially in well-established type 2 diabetes) is less certain.

• Psychosocial factors (e.g., motivation and capacity for self-care) and clinical factors (e.g., age, presence or absence of coexisting conditions, and presence or absence of a tendency toward hypoglycemia) should be considered in setting a target range of glycated hemoglobin for an individual patient.

• A near-normal glycemic target range (6.0 to 6.5%), if implemented safely, could be considered for otherwise healthy patients with recently diagnosed type 2 diabetes and a long life expectancy; more relaxed goals for the glycated hemoglobin level may be preferable in older patients with long-standing type 2 diabetes and cardiovascular disease.

• Lifestyle modification and metformin are recommended as initial therapies for most patients with type 2 diabetes.

• Several therapeutic agents are available when therapy in addition to metformin is needed to control glycemia, but evidence is lacking to support the choice of any one agent over another. Decisions should take into account cost, side effects, and long-term safety and effects on complications of diabetes.
Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Diabetes Care Publish Ahead of Print, published online April 19, 2012
Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy

A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes

D. M. Nathan · J. B. Buse · M. B. Davidson · E. Ferrannini · R. R. Holman · R. Sherwin · B. Zinman
Approach to management of hyperglycemia:

More stringent | Less stringent
--- | ---
Patient attitude and expected treatment efforts | Highly motivated, adherent, excellent self-care capacities | Less motivated, non-adherent, poor self-care capacities
Risks potentially associated with hypoglycemia, other adverse events | Low | High
Disease duration | Newly diagnosed | Long-standing
Life expectancy | Long | Short
Important comorbidities | Absent | Few / mild | Severe
Established vascular complications | Absent | Few / mild | Severe
Resources, support system | Readily available | Limited
Factors that should be considered in determining glycemic goals, including psychosocial limitations (e.g., depression, which is common in patients with type 2 diabetes) and clinical factors, are shown. Characteristics listed in the column at the right warrant the most attention. Despite the strong positive correlation between glycated hemoglobin levels and mean blood glucose levels in populations, blood glucose levels vary at any given level of glycated hemoglobin and glycated hemoglobin values vary at any given blood glucose level. Severe hypoglycemia in patients with type 2 diabetes and cardiovascular disease may lead to myocardial ischemia and may increase the risk of myocardial infarction, cardiac arrhythmias, or sudden death. The intensity of glucose control should be immediately relaxed by an average of approximately 45 to 60 mg per deciliter (glycated hemoglobin by approximately 1.5 to 2.0%) for several weeks after an unexplained severe hypoglycemic episode. More prolonged relaxation of glycemic goals should be considered after two or more episodes. Glycemic targets in patients with “hypoglycemia unawareness” should be relaxed for prolonged periods, pending the potential reversal of the condition. Older patients with impaired cognitive function are prone to severe hypoglycemia, and such episodes may increase the risk of dementia. In general, the older the patient and the longer the duration of the disease, the more established the atherosclerotic process and microvascular derangements, which usually signify less benefit from intensive glycemic treatment. In patients with severe coexisting conditions that could interfere with implementation of the management strategy, the goal is prevention of clinically significant glycosuria, water and electrolyte loss, infections, and the development of nonketotic hyperosmolar coma. Adapted from Ismail-Beigi.
“Evidence-based advice” VS. “Patient-centered care”

- It is patients who make the final decisions regarding
  1. their lifestyle choices
  2. pharmaceutical interventions used
  3. their implementation occurred

- Physician’s role - to synthesis
  1. the best available evidence from the literature
  2. the clinician’s expertise
  3. patient’s own inclinations
Medical management of hyperglycemia in T2DM

Tier 1: Well-validated core therapies

- At diagnosis:
  - Lifestyle + Metformin

  **STEP 1**

- Lifestyle + Metformin + Basal insulin

  **STEP 2**

  - Lifestyle + Metformin + Sulfonylurea

  **STEP 3**

- Lifestyle + Metformin + Intensive insulin

Tier 2: Less well-validated therapies

- Lifestyle + Metformin + Pioglitazone
  - No hypoglycaemia
  - Oedema/CHF
  - Bone loss

- Lifestyle + Metformin + GLP-1 agonist
  - No hypoglycaemia
  - Weight loss
  - Nausea/vomiting

- Lifestyle + Metformin + Basal insulin

- Lifestyle + Metformin + Sulfonylurea
Initial Drug Therapy

- Metformin
- 2 OADs or 1 OAD + insulin
  - If A1C>=9%
- Insulin
  - Strongly suggested, if symptoms (+), AC>=300-350mg/dL, A1C>=10-12%, or ketonuria
  - if symptoms improves (except T1DM) --> may taper insulin partially or entirely with non-insulin drugs or insulin + OAD

*
Stepwise Use of Combination Therapy in Diabetes

糖尿病的胰島素異常

- 胰島素分泌不足（Insulin deficiency）
- 胰島素作用不良（Insulin resistance）
Development of type 2 diabetes

Pre-diabetes

Insulin sensitivity

Insulin secretion

Blood glucose development

Micro-vascular disease

Macro-vascular disease

according to Janka HU, 1992
UKPDS: β-Cell Function for the Patients Remaining on Diet for 6 Years

與糖代謝有關的實驗室及臨床數據

- 糖化血色素(A1C)
- 空腹血糖 (AC sugar)
- 餐後血糖 (PC sugar)
- 血漿C-peptide濃度
- 血漿insulin濃度

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<tr>
<th>A1C (%)</th>
<th>Mean plasma glucose</th>
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<td>mg/dL</td>
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<tr>
<td>6</td>
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<td>7</td>
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http://professional.diabetes.org/eAG
自我血糖監測 (SMBG)

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<th>日期</th>
<th>早餐前</th>
<th>午餐前</th>
<th>午餐後二小時</th>
<th>晚餐前</th>
<th>晚餐後二小時</th>
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<td>152</td>
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</table>
自我血糖監測 (SMBG)
大多數的療法長期使用導致體重增加

UKPDS: 12年高達8公斤
常規治療 (n=411)
Glibenclamide (n=277)
Metformin (n=342)
Insulin (n=409)

ADOPT: 5年高達4.8公斤
Rogiglitazone
Metformin
Glibenclamide

常規治療: 最初採用飲食控制，如果空腹血糖 > 270 mg/dL，則加用SU類、胰島素和/或metformin

以腸促胰素為基礎的治療藥物

胰妥善™ Victoza®
- Liraglutide
  - Human GLP-1 analogues

降爾糖 Byetta
- Exenatide
  - Exendin-based therapies

GLP-1 receptor agonists

Incretin-based therapies

DPP-4 inhibitors

- Sitagliptin 佳糖維 Januvia
- Vildagliptin 高糖優速 Galvus
- Saxagliptin 昂格莎 Onglyza
- Linagliptin 穩斯平 Trajenta

Insulin response is greater following oral glucose than IV glucose, despite similar plasma glucose concentration.

GLP-1 and GIP are Synthesized and Secreted from the Gut in Response to Food Intake

L-cell (ileum)
- Proglucagon
  - GLP-1 [7–37]
  - GLP-1 [7–36 NH₂]

K-cell (jejenum)
- ProGIP
  - GIP [1–42]

GIP=glucose-dependent insulinotropic peptide; GLP-1=glucagon-like peptide-1
Adapted from Drucker DJ. *Diabetes Care.* 2003; 26: 2929–2940.
GLP-1 Demonstrates Multiple Metabolic Effects in Patients with T2DM

GLP-1 decreases PPG and FPG by

- improving α- and β-cell sensitivity to glucose
- delaying gastric emptying
- reducing appetite and food intake
Victoza® 的作用時間較一天兩次的 exenatide 更長。

箭頭指示代表注射時間點。
Decrease of A1C by Liraglutide

Garber et al. Diabetes 2009
Decrease of A1C by Various Agents

<table>
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<tr>
<th>Baseline HbA1c (%)</th>
<th>LEAD-3 Monotherapy</th>
<th>LEAD-2 MET combination</th>
<th>LEAD-1 SU combination</th>
<th>LEAD-4 MET + TZD combination</th>
<th>LEAD-5 MET + SU combination</th>
<th>LEAD-6 MET ± SU combination</th>
<th>Lira vs. sita MET combination</th>
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</thead>
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<tr>
<td>8.3</td>
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<td>8.4</td>
<td>8.4</td>
<td>8.3</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Change in HbA1c for overall population (LEAD-4,-5,-6, Lira vs Sita); add-on to diet and exercise failure (LEAD-3); or add-on to previous OAD monotherapy (LEAD-2,-1). *p<0.01, ***p<0.0001 vs. active comparator. Data from core trials

Benefit of GLP-1 on BW

LEAD-3 Monotherapy
LEAD-2 MET combination
LEAD-1 SU combination MET + TZD combination
LEAD-4 MET + SU combination
LEAD-5 MET ± SU combination
Lira vs. Sita MET combination

Change in body weight (kg)

**Liraglutide 1.2 mg**
**Liraglutide 1.8 mg**
**Rosiglitazone**
**Glimepiride**
**Glargine**
**Placebo**
**Exenatide**
**Sitagliptin**

*p<0.01, ***p≤0.0001 vs. active comparator; †p≤0.01, †††p≤0.0001 vs. placebo. [Active comparators vs. placebo not shown]. Data from core trials

Persistent Benefit of GLP-1 Agonist on BW

- Waist circumference was reduced from baseline by 3.0 cm with liraglutide 1.8 mg
- Waist circumference increased by 0.4 cm with glimepiride ($p<0.0001$)

Garber et al. Lancet 2009; 373: 473–81 (LEAD-3); Garber ADA 2009 (LEAD-3 2 year data)
Inhibition of DPP-4 Increases Active GLP-1

GLP-1 $t_{1/2} = 1–2$ min

GLP-1 inactive (>80% of pool)

Meal → Intestinal GLP-1 release → Active GLP-1 → DPP-4

DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1


Blocking DPP-4 Can Improve Incretin Activity and Correct the Insulin:Glucagon Ratio in T2DM

DPP-4=dipeptidyl peptidase-4; T2DM=type 2 diabetes mellitus
Vildagliptin Enhances GLP-1 Levels in Patients with T2DM

Vildagliptin 100 mg once daily was used in this study. Galvus (vildagliptin) is approved for 50 mg once or twice daily in combination with metformin or a TZD, and Galvus (vildagliptin) 50 mg once daily in combination with a sulfonylurea.

GLP-1 = glucagon-like peptide-1; T2DM = type 2 diabetes mellitus

*P < 0.05.

Vildagliptin Suppresses Glucagon Secretion

Vildagliptin 100 mg once daily was used in this study. Galvus (vildagliptin) is approved for 50 mg once or twice daily in combination with metformin or a TZD, and Galvus (vildagliptin) 50 mg once daily in combination with a sulfonylurea.

*P <0.05 vs placebo.

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## Differences of incretin-based therapies

<table>
<thead>
<tr>
<th>Properties/action</th>
<th>Incretin mimetics</th>
<th>DPP-4 inhibitors</th>
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<tbody>
<tr>
<td>Administration</td>
<td>Subcutaneous</td>
<td>Oral</td>
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<tr>
<td>GLP-1 levels (or equivalent)</td>
<td>Pharmacological (6-10 X)</td>
<td>Physiological (2-3 X)</td>
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<tr>
<td>Main mechanism of GLP-1 receptor stimulation</td>
<td>Interaction with receptors on target organs/cells</td>
<td>Interaction with receptors on afferent nerves (ANS)</td>
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<tr>
<td>Other mediators</td>
<td>No</td>
<td>GIP, PACAP, others (questionable)</td>
</tr>
<tr>
<td>Effects on gastric emptying</td>
<td>Yes</td>
<td>No (hardly)</td>
</tr>
<tr>
<td>Effects on appetite</td>
<td>Reduced</td>
<td>Hardly influenced</td>
</tr>
<tr>
<td>Effects on body weight</td>
<td>Weight loss</td>
<td>Weight neutrality</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Nausea, vomiting, antibodies (exenatide, relevance?), pancreatitis (causal relation?)</td>
<td>Upper respiratory tract infections, elevations in liver enzymes (vildagliptin), skin reactions (sitagliptin)</td>
</tr>
</tbody>
</table>

*Diabetes Care 32(suppl 2):S223-S231, 2009.*
口服抗糖尿病药物
Oral Antidiabetic Drugs (OAD)
口服降血糖藥物的種類

- 胰島素分泌促進劑 (insulin secretagogues)
  - 磺醯尿素 (sulfonylureas)
  - Glinides (又稱 Meglitinides 類似物)

- 胰島素敏感劑 (insulin sensitizer)
  - 雙胍類 (Biguanides)
  - Glitazones (Thiazolidinediones, TZD)

- 阿爾發－葡萄糖甘酶抑制劑 (α-glucosidase inhibitor)
- 二肽基肽酶抑制劑 (DPP-4 Inhibitor)
Major Targeted Sites of Oral Drug Classes

DPP-4 = dipeptidyl peptidase 4; TZDs = thiazolidinediones.

<table>
<thead>
<tr>
<th>學名</th>
<th>商品名</th>
<th>劑量範圍 (mg/day)</th>
<th>Peak level (h)</th>
<th>Half-life (h)</th>
<th>代謝途徑 (腎/肝)</th>
<th>健保價 (元)</th>
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<td>Glipizide</td>
<td>GliDiab</td>
<td>2.5-40</td>
<td>1-3</td>
<td>2-4</td>
<td>80/20</td>
<td>1.5/ 5mg</td>
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<tr>
<td>Gliclazide</td>
<td>Mezide</td>
<td>80-320</td>
<td>4–6</td>
<td>10.4</td>
<td>65/25</td>
<td>1.78/ 80mg</td>
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<tr>
<td>Glibenclamide</td>
<td>Gliben</td>
<td>1.25-20</td>
<td>~4</td>
<td>10</td>
<td>50/50</td>
<td>1.5/ 5mg</td>
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<td>Glimepiride</td>
<td>Amaryl</td>
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<td>2-3</td>
<td>9</td>
<td>60/40</td>
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<td>Repaglinide</td>
<td>Novonorm</td>
<td>1.5-12</td>
<td>0.75</td>
<td>1</td>
<td>-/100</td>
<td>4.98/ 1mg</td>
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<tr>
<td>Nateglinide</td>
<td>Starlix</td>
<td>360</td>
<td>1.0</td>
<td>1.4</td>
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<td>6.5/ 120mg</td>
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*成大醫院現有之口服降血糖藥物 (1)*
<table>
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<tr>
<th>學名</th>
<th>商品名</th>
<th>劑量範圍 (mg/day)</th>
<th>Peak level (h)</th>
<th>Half-life (h)</th>
<th>代謝途徑 (腎/肝)</th>
<th>健保價 (元)</th>
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<td>6</td>
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<td>1 ~ 4</td>
<td>12.4</td>
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<td>34/ 100mg</td>
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選擇口服降血糖藥物之考量原則

需依據患者之病情

- 胰島素分泌不足 (Insulin deficiency) 或胰島素作用不良 (Insulin resistance)？
- 血糖之高低與糖尿病症狀之嚴重程度
- 飲食習慣與進食狀況
- 肝、腎、心臟功能與併發之疾病
- 自理生活之能力與居家照顧之品質
- 藥物之療效
- 低血糖等副作用的風險
- 價格因素
選擇胰島素分泌促進劑的原則

- 促胰島素分泌能力
- 藥物起始作用時間
- 藥效之長短
- 代謝與排泄途徑
- 副作用與使用禁忌
- 除胰臟外之效應
- 藥物交互作用
胰島素分泌促進劑

- 磺醯尿素(sulfonylureas)
  - A1C 降低約1-2%
  - 最大降糖效果通常在仿單建議最大劑量的1/2~2/3時便已達到

- Glinides (Meglitinides analogue)
  - A1C 降低約0.8%
  - 作用快速，須隨餐服用，可降低餐後高血糖
  - 短效，較少低血糖副作用
  - Repaglinide 不可與gemfibrozil 併用
SU的作用機轉

1. 硫醯基尿素類藥物與ATP 鈣通道上或附近的受體結合。
2. 鈣通道關閉
3. 促使鈣通道打開，鈣流入細胞中
4. 胰島素被釋放到血液中。
低血糖副作用及策略

危险因子
- 老年、营养状况不佳、餐无定时、或合并有肝肾功能异常者

低剂量起始
- 高危险族群考虑使用glinide

肾功能不良者考虑短效、具不活性代谢物、由肝脏排除者尤佳，可使用glinide

餐无定时或常误餐者，可使用glinide

注意药物交互作用
- Alcohol, anticoagulant, trimethoprim
Metformin

- 常用於過重或肥胖的(準)糖尿病患者
- 並不刺激胰島素分泌，單獨使用少見低血糖副作用
- 抑制肝糖新生與製造，因而降低空腹血糖
- 治療後不會增加體重
- 可改善血脂肪異常，對內皮細胞功能等心血管危險因子有正向的影響
- 常見腸胃道一過性副作用，低劑量起始可避免
- 肝腎心肺功能不良不宜使用，以免發生代謝性酸中毒
- Creatinine>1.5(男); >1.4(女) 不建議使用 (?)
Titration of metformin

1. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day

2. After 5–7 days, if gastrointestinal (GI) side effects have not occurred, advance dose to 850, or two 500 mg tablets, twice per day. Medication to be taken before breakfast and/or dinner

3. If GI side effects appear as doses advanced, decrease to previous lower dose and try to advance the dose at a later time

4. The maximum effective dose can be up to 1,000 mg twice per day, but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. GI side effects may limit the dose that can be used

5. Based on cost considerations, generic metformin is the first choice of therapy. A longer acting formulation is available in some countries and can be given once per day
Biguanide(雙胍類)的作用機轉

1. Metformin降低肝臟中的葡萄糖新生作用

2. 降低或延遲腸道葡萄糖吸收

3. 促進GLUT4移動到細胞表面而增加胰島素敏感性

取材自 Harmel et al, 2004; Glucophage SPC, 2004; Tortora et al, 2003
Acarbose

-抑制近端小腸澱粉及雙醣類之分解，延緩葡萄糖的吸收，降低飯後血糖、胰島素濃度，甚至空腹血糖
-不被腸胃道吸收(<1%)
-無體重增加之副作用
-副作用為輕至中度的脹氣、腹瀉；自低劑量起始可減緩(start low, go slow)
-低血糖僅出現於合併療法時，須使用葡萄糖或牛奶治療
-使用於輕中度糖尿病之單一治療或合併治療
-可減低葡萄糖耐量異常患者轉變為第2型糖尿病的機率及發生心血管疾患的風險，減緩頸動脈內膜厚度增加速率 (STOP-NIDDM)
-可減低第2型糖尿病患者心肌梗塞風險(MeRIA)
Acarbose: mechanism of action

Competitive inhibition of the intestinal enzymatic hydrolysis of oligosaccharides

Acarbose

Starch oligosaccharides

Oligosaccharides

Acarbose

Microvillus

α-glucosidase

Glucose

Microvilli

Enterocyte
Retardation of carbohydrate absorption under acarbose

Without acarbose

With acarbose

Carbohydrate resorption in the duodenum, jejunum, and ileum without and with acarbose.
Thiazolidinediones

- 活化peroxisome proliferative-activated receptor-γ (PPAR-γ), 而增加胰島素之敏感度, 降低空腹血糖及血中胰島素濃度
- 降糖效果較緩慢, 通常需6至8週才見成效
- 需在內生或外源性胰島素存在下才有作用
- 可改善內皮細胞功能, 發炎指標等心血管疾患危險因子
- 與metformin 併用對改善胰島素阻抗性有加成作用
- 常見副作用有體重增加、水腫等, 需密切追蹤肝指數如ALT, 若ALT值超過正常上限的三倍, 應停藥
- 重度心臟衰竭者不宜使用
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Expected decrease in A1C (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>1-2</td>
<td>Inexpensive</td>
<td>Weight gain, hypoglycemia</td>
</tr>
<tr>
<td>Metformin</td>
<td>1-2</td>
<td>Weight neutral, inexpensive</td>
<td>GI side effects, rare lactic acidosis</td>
</tr>
<tr>
<td>Thiazolidinediones (glitazones)</td>
<td>0.5-1.4</td>
<td>Improved lipid profile†,</td>
<td>Fluid retention, risk of CHF, potential risk of MI, weight gain, atherogenic lipid profile,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potential decreased risk of MI†</td>
<td>expensive</td>
</tr>
<tr>
<td>Glinides</td>
<td>0.5-1.5</td>
<td>Short duration</td>
<td>Thrice daily dosing, expensive, hypoglycemia</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>0.5-0.8</td>
<td>Weight neutral</td>
<td>Frequent GI side effects, thrice daily dosing</td>
</tr>
<tr>
<td>DPP4-inhibitor</td>
<td>0.5-0.8</td>
<td>Weight neutral</td>
<td>Little experience, expensive</td>
</tr>
</tbody>
</table>

Nathan et al. Diabetes Care 31:173-175, 2008*
Cumulative Incidence of Monotherapy Failure

Patients at Risk
Rosiglitazone 139 120 107 95 84 32
Metformin 139 120 107 95 81 31
Glyburide 7 5 6 0 8 1

糖尿病藥物合併治療之原則

- 合併口服降糖藥物 或 口服降糖藥物併用胰島素
- 合併治療優於最大劑量的單一治療
- 具相同機轉的單一治療藥物間之轉換少見成效
- 應併用不同作用機轉藥物
- 併用口服降糖藥物不宜超過3種
- 適時加入胰島素合併治療
Combinations of Oral Agents Used to Treat T2DM

<table>
<thead>
<tr>
<th>Combinations</th>
<th>Expected Decrease from Addition of Second Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FPG (mg/dl)</td>
</tr>
<tr>
<td>Rosiglitazone + metformin</td>
<td>53 (3.0)</td>
</tr>
<tr>
<td>Pioglitazone + metformin</td>
<td>38 (2.1)</td>
</tr>
<tr>
<td>Acarbose + metformin</td>
<td>10 (0.5)</td>
</tr>
</tbody>
</table>

*Supported by peer-reviewed publications*

On average, any second agent is typically associated with an approximate further reduction in A1C of $\sim 1\%$.
Treating fasting hyperglycemia lowers the entire 24-hour plasma glucose profile

Comparison of 24-hour glucose levels in control subjects vs patients with diabetes (p<0.001).
Comparison of 24-hour glucose levels in control subjects vs patients with diabetes (p<0.001).


Treating fasting hyperglycemia lowers the entire 24-hour plasma glucose profile.
胰島素合併口服降血糖藥物治療的好處

- 容易衛教
- 不需混合使用胰島素
- 於門診時容易使用
- 病患配合度高
- 心理調適容易
- 較少胰島素劑量
<table>
<thead>
<tr>
<th>Schedule</th>
<th>Dose</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 x Basal</strong></td>
<td>10 IU</td>
<td>bedtime</td>
</tr>
<tr>
<td><strong>FBG value in milli moles per liter</strong></td>
<td>0.16 IU/Kg</td>
<td></td>
</tr>
<tr>
<td><strong>1 x Premix</strong></td>
<td>10 IU</td>
<td>Pre supper</td>
</tr>
<tr>
<td><strong>2 x Premix</strong></td>
<td>10 IU</td>
<td>Pre breakfast, 10 IU</td>
</tr>
<tr>
<td><strong>MDI</strong></td>
<td>Individualized</td>
<td></td>
</tr>
</tbody>
</table>
Scheme for Adding Basal or Intermediate-Acting Insulin to Oral Agents

Start with 10 units of basal (glargine) or intermediate-acting (NPH) insulin at bedtime (~10:00 p.m.). Adjust insulin dose weekly according to the following guidelines.

<table>
<thead>
<tr>
<th>Self-monitored FPG (mg/dl)</th>
<th>Increase in insulin dose (units/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥180</td>
<td>8</td>
</tr>
<tr>
<td>≥140 but &lt;180</td>
<td>6</td>
</tr>
<tr>
<td>≥120 but &lt;140</td>
<td>4</td>
</tr>
<tr>
<td>≥100 but &lt;120</td>
<td>2</td>
</tr>
</tbody>
</table>

Treat-to-target FPG ≤100 mg/dl

Do not increase insulin dose if FPG is <72 mg/dl on 2 days. Decrease insulin dose 2–4 units/day if FPG is <56 mg/dl or clinically significant hypoglycemia occurs.

Start with 5–10 units; increase by 2–3 units every 3 days until FPG is between 110 and 120 mg/dl
## Clinic- vs. Patient-driven Titration of Basal Insulin --AT.LANTUS Study

<table>
<thead>
<tr>
<th>Mean FBG for the previous 3 consecutive days</th>
<th>Increase in daily basal insulin glargine dose (U)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algorithm 1: Clinic-driven titration at every visit</td>
<td>Algorithm 2: Patient-driven titration every 3 days</td>
</tr>
<tr>
<td>≥100 and &lt;120 mg/dl (≥5.5 and &lt;6.7 mmol/l)</td>
<td>0–2</td>
</tr>
<tr>
<td>≥120 and &lt;140 mg/dl (≥6.7 and &lt;7.8 mmol/l)</td>
<td>2</td>
</tr>
<tr>
<td>≥140 and &lt;180 mg/dl (≥7.8 and &lt;10 mmol/l)</td>
<td>4</td>
</tr>
<tr>
<td>≥180 mg/dl (≥10 mmol/l)</td>
<td>6–8</td>
</tr>
</tbody>
</table>

Self-Titration of Insulin Detemir: The PREDICTIVE 303 Study

- 303 Algorithm Sites: Patients to adjust dose every 3 days based on mean FPG values

<table>
<thead>
<tr>
<th>FPG (mg/dL)</th>
<th>Basal Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 80</td>
<td>Reduce detemir dose by 3U</td>
</tr>
<tr>
<td>80-110</td>
<td>No change</td>
</tr>
<tr>
<td>&gt;110</td>
<td>Increase detemir dose by 3U</td>
</tr>
</tbody>
</table>

- Standard-of-Care sites: Physician to adjust dose based on standard-of-care

Meneghini et al. Diabetes Obes Metab. 2007; 9:902-13
胰島素及類似物
(Insulin and insulin analogue)
正常人血糖與胰島素濃度曲線

Continuous basal insulin secretion
Incremental prandial insulin secretion
Normal Insulin Secretion Profile

Plasma insulin (µU/mL)

- Breakfast
- Lunch
- Dinner

4:00 8:00 12:00 16:00 20:00 24:00 4:00 8:00

Time
Ideal Insulin Replacement Pattern

Plasma insulin (µU/mL)

Time

Breakfast
Lunch
Dinner

Basal
Mealtime
Idealized Profiles of Fast-Acting Insulins

Idealized Profiles of Basal Insulins

何時需使用胰島素?

- 第1型糖尿病患者
- 第2型糖尿病患者
- 空腹血糖超過300 毫克/毫升 和合併酮體血症或酮體尿症。
- 持續性出現空腹血糖超過 300 毫克/毫升 和出現多尿、多喝、及體重減輕的症狀
- 糖尿病酮酸血症患者
- 肝腎功能不良的糖尿病患者
- 因急性病症住院的糖尿病或高血糖患者
- 口服抗糖尿病藥物療效不佳者
- 願意接受胰島素做為第一線治療的患者
- 妊娠性糖尿病患者無法以飲食控制者
- 糖尿病婦女懷孕時
Recognizing Oral Therapy Inadequacy

- When A1C is not at goal of 7% and:
  - 2 OADs being used-maximally
  - Increased hyperglycemic symptoms, weight loss
  - SMBG shows significant fasting hyperglycemia >200 mg/dL and/or day-long up to 300 mg/dL
  - Duration of diabetes >5 years
  - Low C-peptide
  - Physiologic stress

- Therapeutic Decision:
  - Add third oral medication (anticipate A1C↓ 1-1.5%)
  - Add exenatide to sulfonylurea and metformin
  - Start insulin
After Basal Insulin added,

Keep metformin

Maintain secretagogues, avoid when prandial insulin added

TZD should be reduced (or stopped) except for sever IR with large insulin requirement
Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes

Rury R. Holman, M.B., Ch.B., F.R.C.P., Kerensa I. Thorne, M.Sc.,
Andrew J. Farmer, D.M., F.R.C.G.P., Melanie J. Davies, M.D., F.R.C.P.,
Joanne F. Keenan, B.A., Sanjoy Paul, Ph.D., and Jonathan C. Levy, M.D., F.R.C.P.,
for the 4-T Study Group*
Changes of A1C

Max. reduction occurred at 24 weeks and remained stable

Comparisons between Changes of Glycemic Variables and Adverse Effects

Changes in A1C - BID vs. TID BIAsp30

Subjects Achieving A1C Targets
- BID vs. TID BIAsp30

O.R. = 0.48, P<0.005
O.R. = 0.57, P<0.022
O.R. = 1.69, P<0.010
O.R. = 2.19, P<0.013

Main Cohort
Baseline A1C ≥ 9%

Basal-bolus Therapy Attempts to Re-create Physiological Insulin Secretion

Predicted plasma insulin concentration profile (mU/l)

- Rapid-acting insulin
- Basal insulin
- Total

Time of day

6 10 14 18 22 2 6

Predicted plasma insulin concentration profile (mU/l)
Insulin Pump
The insulin pump delivers basal and bolus insulin precisely and can be easily customized as needed to meet individual requirements.

Programmable Insulin Delivery with Medtronic MiniMed Pump Therapy

- **Basal insulin delivery**
- **Bolus insulin delivery**

- **Basal programmed to help prevent dawn phenomenon**
- **Dual Wave™ Bolus for brunch**
- **Temporary basal during walking to help prevent hypoglycemia**
- **Dinner bolus**
- **Basal reduced to help prevent nocturnal hypoglycemia**
Correlation Between Urinary 8-iso-PGF2α and Glucose Variability (MAGE) in T2DM

R=0.86, p<0.0001

JAMA 295:1688-97, 2006
Activation of oxidative stress leads to glucose fluctuations (MAGE) and increased risk of complications.
Sequential Insulin Strategies in Type 2 Diabetes

Non-insulin regimens

Basal insulin only (usually with oral agents)

Basal insulin + 1 (mealtime) rapid-acting insulin injection

Basal insulin + ≥2 (mealtime) rapid-acting insulin injections

Pre-mixed insulin twice daily

Number of injections

1
Low

2
Mod.

3+
High

Regimen complexity

More flexible

Less flexible

Flexibility

Diabetes Care Publish Ahead of Print, published online April 19, 2012
<table>
<thead>
<tr>
<th>Class</th>
<th>Compound(s)</th>
<th>Cellular mechanism</th>
<th>Primary physiological action(s)</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>Activates AMP-kinase</td>
<td>↓ Hepatic glucose production</td>
<td>Extensive experience, no weight gain, no hypoglycemia, likely ↓ CVD events (UKPDS)</td>
<td>Gastrointestinal side effects (diarrhea, abdominal cramping), lactic acidosis risk (rare), Vitamin B₁₂ deficiency, multiple contraindications: CKD, acidosis, hypoxia, dehydration, etc.</td>
<td>Low</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>2nd generation</td>
<td>Closes K₅ ATP channels on β-cell plasma membranes</td>
<td>↑ Insulin secretion</td>
<td>Extensive experience, ↓ Microvascular risk (UKPDS)</td>
<td>Hypoglycemia, weight gain, ↓ Blunts myocardial ischemic preconditioning, low durability</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Glyburide/</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>glibenclamide</td>
<td></td>
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<tr>
<td></td>
<td>Glipizide</td>
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<tr>
<td></td>
<td>Gliclazide</td>
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<tr>
<td></td>
<td>Glimepiride</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meglitinides (glitazones)</td>
<td>Repaglinide</td>
<td>Closes K₅ ATP channels on β-cell plasma membranes</td>
<td>↑ Insulin secretion</td>
<td>↓ Postprandial glucose excursions, dosing flexibility</td>
<td>Hypoglycemia, weight gain, ↓ Blunts myocardial ischemic preconditioning, frequent dosing schedule</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Nateglinide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Pioglitazone</td>
<td>Activates the nuclear transcription factor PPAR-γ</td>
<td>↑ Insulin sensitivity</td>
<td>No hypoglycemia, durability, ↑ HDL-C, ↓ Triglycerides (pioglitazone), ↑ LDL-C (rosiglitazone), ↑ MI (meta-analyses, rosiglitazone), ↑ Bladder cancer (pioglitazone)</td>
<td>Weight gain, edema/heart failure, bone fractures, ↑ LDL-C (rosiglitazone), ↑ MI (meta-analyses, rosiglitazone), ↑ Bladder cancer (pioglitazone)</td>
<td>High*</td>
</tr>
<tr>
<td></td>
<td>Rosiglitazone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>Acarbose</td>
<td>Inhibits intestinal α-glucosidase</td>
<td>Slows intestinal carbohydrate digestion/absorption</td>
<td>No hypoglycemia, ↓ Postprandial glucose excursions, ↑ ↓ CVD events (ProACTIVE, pioglitazone)</td>
<td>Generally modest HbA₁c efficacy, gastrointestinal side effects (flatulence, diarrhea), frequent dosing schedule</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Miglitol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Voglibose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Sitagliptin</td>
<td>Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations</td>
<td>↑ Insulin secretion (glucose-dependent), ↓ Glucagon secretion (glucose-dependent)</td>
<td>No hypoglycemia, well tolerated</td>
<td>Generally modest HbA₁c efficacy, urticaria/angioedema, ↑ Pancreatitis</td>
<td>High</td>
</tr>
<tr>
<td>Class</td>
<td>Compound(s)</td>
<td>Cellular mechanism</td>
<td>Primary physiological action(s)</td>
<td>Advantages</td>
<td>Disadvantages</td>
<td>Cost</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>----------------------------------</td>
<td>-------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>• Colesevelam</td>
<td>Binds bile acids in intestinal tract, increasing hepatic bile acid production; ? activation of farnesoid X receptor (FXR) in liver</td>
<td>• Unknown</td>
<td>No hypoglycemia</td>
<td>Generated modest HbA1c efficacy</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ↓ Hepatic glucose production</td>
<td>↓ LDL-C</td>
<td>Constitipation, ↑ Triglycerides, May ↓ absorption of other medications</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ↑ Incretin levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine-2 agonists</td>
<td>• Bromocriptine (quick-release)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Activates dopaminergic receptors</td>
<td>• Modulates hypothalamic regulation of metabolism</td>
<td>No hypoglycemia</td>
<td>Generally modest HbA1c efficacy</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ↑ Insulin sensitivity</td>
<td></td>
<td>Dizziness/syncope, Nausea, Fatigue, Rhinitis</td>
<td></td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>• Exenatide</td>
<td>Activates GLP-1 receptors</td>
<td>• ↑ Insulin secretion (glucose-dependent)</td>
<td>No hypoglycemia</td>
<td>Gastrointestinal side effects (nausea/vomiting)</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>• Exenatide extended release</td>
<td></td>
<td>• ↓ Glucagon secretion (glucose-dependent)</td>
<td>Weight reduction</td>
<td>Acute pancreatitis, C-cell hyperplasia/medullary thyroid tumors in animals</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Liraglutide</td>
<td></td>
<td>• Slows gastric emptying</td>
<td>? Potential for improved β-cell mass/function</td>
<td>Injectable</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ↑ Satiety</td>
<td>? Cardiovascular protective actions</td>
<td>Training requirements</td>
<td></td>
</tr>
<tr>
<td>Amylin mimetics</td>
<td>• Pramlintide&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Activates amylin receptors</td>
<td>• ↓ Glucagon secretion</td>
<td>↓ Postprandial glucose excursions</td>
<td>Generally modest HbA1c efficacy</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Slows gastric emptying</td>
<td>Weight reduction</td>
<td>Gastrointestinal side effects (nausea/vomiting)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ↑ Satiety</td>
<td></td>
<td>Hypoglycemia unless insulin dose is simultaneously reduced</td>
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<td></td>
<td>Injectable, Frequent dosing schedule</td>
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<tr>
<td>Insulins</td>
<td>• Human NPH</td>
<td>Activates insulin receptors</td>
<td>• ↑ Glucose disposal</td>
<td>Universally effective</td>
<td>Hypoglycemia</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>• Human Regular</td>
<td></td>
<td>• ↓ Hepatic glucose production</td>
<td>Theoretically unlimited efficacy</td>
<td>Weight gain</td>
<td></td>
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<td></td>
<td>• Lispro</td>
<td></td>
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<td>? Mitogenic effects</td>
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<td>• Aspart</td>
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<td>Injectable</td>
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<td></td>
<td>• Glulisine</td>
<td></td>
<td></td>
<td></td>
<td>Training requirements</td>
<td></td>
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<td></td>
<td>• Glargine</td>
<td></td>
<td></td>
<td></td>
<td>“Stigma” (for patients)</td>
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<td></td>
<td>• Detemir</td>
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<tr>
<td></td>
<td>• Premixed (several types)</td>
<td></td>
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</tbody>
</table>

<sup>a</sup>Limited use in the U.S./Europe. <sup>b</sup>Not licensed in the U.S. <sup>c</sup>Prescribing highly restricted in the U.S.; withdrawn in Europe. <sup>d</sup>Not licensed in Europe. <sup>e</sup>To be available as a generic product in 2012, with expected significant reductions in cost. <sup>f</sup>Depends on type (analog = human insulin) and dosage. CKD, chronic kidney disease; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; GLP-1, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; PPAR, peroxisome proliferator-activated receptor; ProACTIVE, Prospective Pioglitazone Clinical Trial in Macrovascular Events (60); STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (134); UKPDS, UK Prospective Diabetes Study (29–33).
Hyperglycemia in Type 2 Diabetes

- Increased Hepatic Glucose Production: Weight loss, exercise, biguanides, insulin, thiazolidinediones, possibly bile acid sequestrants
- Increased Glucagon Secretion: GLP-1–receptor agonists, DPP-IV inhibitors, amylin mimetics
- Increased Appetite: GLP-1–receptor agonists, amylin mimetics
- Increased Insulin Resistance: Weight loss, exercise, biguanides, thiazolidinediones, D2 dopamine–receptor agonists
- Decreased Insulin Secretion: Sulfonylureas, meglitinides, GLP-1–receptor agonists, DPP-IV inhibitors
- Increased Rate of Gastric Emptying: GLP-1–receptor agonists, amylin mimetics
- Carbohydrate Absorption: Alpha-glucosidase inhibitors
- Decreased Amylin Secretion: Amylin mimetics
- Impaired Incretin Effect: GLP-1–receptor agonists, DPP-IV inhibitors, possibly bile acid sequestrants

KEY POINTS

- Glycemic targets and glucose-lowering therapies must be individualized.
- Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program.
- Unless there are prevalent contraindications, metformin is the optimal first-line drug.
- After metformin, there are limited data to guide us. Combination therapy with an additional 1–2 oral or injectable agents is reasonable, aiming to minimize side effects where possible.
- Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control.
- All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values.
- Comprehensive cardiovascular risk reduction must be a major focus of therapy.
案例 討論
案例一

- 46歲女性，糖尿病史2年

- 主訴：服藥後“飢餓感增加，似低血糖”，但自量血糖180 mg/dL

- 身高：160公分；體重：59公斤；BMI：23.0

- 實驗室檢查：
  - AC: 210 mg/dL；A1C: 9.8% (3月前11.0%)

- 目前用藥：
  - Glimepiride 4 mg/day

- 醫師處置：
  - Glimepiride 減量至 2 mg/day
案例二

● 39歲男性，無糖尿病史

● 主訴: 三多，3個月體重減輕7公斤

● 身高: 170公分; 體重: 60.5公斤; BMI: 20.9

● 實驗室檢查:
  ● AC: 360 mg/dL,  A1C: 12.0%

● 醫師處置:
  ● Glibenclamide 15 mg/day, metformin 1500 mg/day
案例三

- 83歲男性，糖尿病史10年，規則控制

- 主訴：最近2個月常發抖、盜汗；就診日於清晨運動時無預兆跌倒

- 身高：157公分；體重：63公斤；BMI：25.6

- 實驗室檢查：
  - AC: 72 mg/dL (3個月前145 mg/dL, 半年前102 mg/dL); A1C: 5.9% (半年前6.4%)

- 目前用藥：
  - Glibenclamide 5 mg bid (6個月前5 mg qd)
案例四

- 65歲女性，糖尿病史13年，規則控制

- 主訴: 最近3個月血糖偏高，不易控制

- 身高: 161公分；體重: 59公斤；BMI: 22.8

- 實驗室檢查:
  - SMBG: 空腹170–200 mg/dL，餐後210–280 mg/dL
  - AC: 195 mg/dL (3個月前180 mg/dL)；A1C: 10.4%（半年前8.6%）

- 目前用藥:
  - Glipizide 5 mg tid, metformin 1000 mg bid, pioglitazone 30 mg qd

- 醫師處置:
  - Glimepiride 6 mg qd, metformin 1000 mg bid, sitagliptin 100 mg qd
A 39-year-old man with a 2-year history of type 2 diabetes mellitus presents for care. He has no microvascular or macrovascular complications. His family history is positive for type 2 diabetes and cardiovascular disease in his mother and older brother. On examination, his weight is 99.8 kg (220 lb), with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 37, and his blood pressure is 125/85 mm Hg. His glycated hemoglobin level is 8.9%, serum creatinine level 1.0 mg per deciliter (88.4 μmol per liter), low-density lipoprotein (LDL) cholesterol 88 mg per deciliter (2.3 mmol per liter), high-density lipoprotein (HDL) cholesterol 45 mg per deciliter (1.2 mmol per liter), and triglyceride level 130 mg per deciliter (1.5 mmol per liter); he does not have microalbuminuria. His medications include metformin (500 mg twice daily), glipizide (5 mg twice daily), simvastatin (20 mg daily), and lisinopril (10 mg daily). What would you recommend to improve his glycemic control?
Thanks for Your Attention