Case study:

Adult with uncontrolled type 2 diabetes of long duration and cardiovascular disease

Authored by Paul Zimmet and Richard Nesto on behalf of the Global Partnership for Effective Diabetes Management.

The Global Partnership for Effective Diabetes Management is supported by an unrestricted educational grant from Bristol-Myers Squibb, AstraZeneca LP.
• This case study outlines the treatment of an adult who has uncontrolled diabetes of long duration and cardiovascular disease

• The case reflects a full range of treatment and management tools available in the European/US context*

*The management of any patient is subject to social, economic, gender, age, co-morbidity and ethnic variables, and is dependent on the range of treatment options available in specific regions or countries.
Adult with uncontrolled diabetes of long duration and CVD

• Eileen, 64, lives with her partner and has four adult children
• She was diagnosed with type 2 diabetes 5 years ago and with stable angina 3 years ago
• She works on a supermarket checkout 3 days per week
• Eileen had good glycaemic control for many years, but has recently been struggling to achieve her HbA₁c target of 6.5–7.0%
• At Eileen’s last visit, a third anti-hyperglycaemic medication was added to her regimen
  – Hyperglycaemia was not marked and required reduction in HbA₁c was <1%

Current medications
• Metformin extended release 2000 mg daily
• Sitagliptin 100 mg daily
• Glipizide 5 mg daily
• Ramipril 5 mg b.i.d.
• Atorvastatin 80 mg daily
• Glyceryl trinitrate spray
  • 400 µg x 2 as needed
• Propranolol 80 mg b.i.d.
• ASA 75 mg daily

ASA, acetylsalicylic acid; b.i.d., twice daily.
Clinical chemistry on consecutive visits

Current visit
- FPG: 10.0 mmol/l
- HbA\(_{1c}\): 7.8%
- LDL-cholesterol: 1.1 mmol/l
- HDL-cholesterol: 1.5 mmol/l
- Triglycerides: 1.2 mmol/l
- BP: 128/77 mmHg
- BMI: 32 kg/m\(^2\)

Previous visit 3 months ago (normal range)
- FPG: 10.2 mmol/l (3.9–5.5 mmol/l)
- HbA\(_{1c}\): 7.9% (4.0–6.0%)
- LDL-cholesterol: 1.2 mmol/l (<2.6 mmol/l)
- HDL-cholesterol: 1.5 mmol/l (>1.5 mmol/l)
- Triglycerides: 1.3 mmol/l (<1.7 mmol/l)
- Blood pressure: 126/78 mmHg (120/80 mmHg)
- BMI: 32 kg/m\(^2\) (18.5–24.9 kg/m\(^2\))

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- Metformin extended release 2000 mg daily
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ASA, acetylsalicylic acid; b.i.d., twice daily; BMI, body mass index; FPG, fasting plasma glucose; HbA\(_{1c}\), glycosylated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein.
### Clinical chemistry on consecutive visits

#### Previous visit 3 months ago (normal range)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>184 mg/dl</td>
<td>70–100 mg/dl</td>
</tr>
<tr>
<td>HbA1c</td>
<td>64 mmol/mol</td>
<td>20–42 mmol/mol</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>46 mg/dl</td>
<td>&lt;100 mg/dl</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>58 mg/dl</td>
<td>&gt;60 mg/dl</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>115 mg/dl</td>
<td>&lt;150 mg/dl</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>126/78 mmHg</td>
<td>120/80 mmHg</td>
</tr>
<tr>
<td>BMI</td>
<td>32 kg/m²</td>
<td>18.5–24.9 kg/m²</td>
</tr>
</tbody>
</table>

#### Current visit

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>180 mg/dl</td>
</tr>
<tr>
<td>HbA1c</td>
<td>62 mmol/mol</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>43 mg/dl</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>58 mg/dl</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>106 mg/dl</td>
</tr>
<tr>
<td>BP</td>
<td>128/77 mmHg</td>
</tr>
<tr>
<td>BMI</td>
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</tbody>
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### Current medications

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ASA, acetylsalicylic acid; b.i.d., twice daily; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycosylated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein.
Reason for poor glycaemic control

• Eileen’s current medication is failing to control her hyperglycaemia. The doctor discusses with Eileen the possible reasons for this
• Eileen reports no side effects of therapy and shows the doctor her timetable for taking her medication
• She also says that she is maintaining good eating habits, but admits she is not doing as much physical activity as she was 3 months ago
• The doctor asks Eileen how well she sleeps, and if she ever experiences morning headaches, an inability to focus or irritability
• Eileen says she tends to sleep through the night without much disturbance, and doesn’t feel tired until the end of the day

Question
What is the most likely explanation for Eileen’s inadequate glycaemic control?

- Poor adherence to medication
- Reduced β-cell function
- Poor adherence to exercise regimen
- Obstructive sleep apnoea
Reason for poor glycaemic control

**Question**
What is the most likely explanation for Eileen’s inadequate glycaemic control?

- Poor adherence to medication
- Reduced β-cell function
- Poor adherence to exercise regimen
- Obstructive sleep apnoea

- Eileen is organized, motivated and reports no side effects of therapy; poor adherence to medication is unlikely to be causing her poor glycaemic control.
- Eileen’s lack of physical activity is a recent occurrence, and is unlikely to account for poor glycaemic control during the past year.
- Obstructive sleep apnoea is strongly associated with type 2 diabetes and obesity,¹ and has been shown to have adverse effects on glycaemic control²
  - However, Eileen does not appear to have any symptoms of this.
- Type 2 diabetes is associated with progressive loss of β cells and β-cell function³
- In those patients with long-standing disease, who are no longer attaining glycaemic targets despite good adherence to medication, loss of β cells and β-cell function should be considered as an explanation for poor glycaemic control.

Response to poor glycaemic control

- The doctor explains to Eileen that her antihyperglycaemic medication requires adjustment.
- He also stresses the importance of adhering to lifestyle interventions in order to re-establish good glycaemic control.

**Question**
Which of the following is an appropriate next course of action for Eileen?

- Intensify the dose of sulphonylurea
- Add basal insulin to Eileen’s existing regimen
- Begin basal insulin but discontinue other therapies
Option selected: Increase the dose of sulphonylurea

- Sulphonylureas enhance insulin release from β cells\(^1\)
- Eileen’s long duration of diabetes and lack of response to current medication suggest advanced β cell loss, leading to impaired insulin production
- Increasing the dose of sulphonylurea is unlikely to be an effective solution for Eileen

<table>
<thead>
<tr>
<th>Antihyperglycaemic agent</th>
<th>Primary physiological action(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>• Decreases hepatic glucose production</td>
</tr>
<tr>
<td>Sulphonylurea</td>
<td>• Increases insulin secretion</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>• Increases insulin secretion</td>
</tr>
<tr>
<td></td>
<td>• Decreases glucagon secretion (both glucose dependent)</td>
</tr>
<tr>
<td>Insulin</td>
<td>• Increases glucose disposal</td>
</tr>
<tr>
<td></td>
<td>• Decreases hepatic glucose production</td>
</tr>
</tbody>
</table>

A priority for Eileen is to lower her HbA$_{1c}$ while also ensuring her safety.

Uncontrolled hyperglycaemia together with CVD place her at high risk for complications.

Therapies other than insulin are unlikely to provide sufficient benefit:

1. Eileen has long-standing diabetes and has not responded to a third oral agent: when triple oral therapy proves unsuccessful, the approach should be rapidly reconsidered.

2. There is no evidence to support the continued use of sulphonylureas with insulin.

3. However, metformin may minimize the weight gain associated with insulin therapy and has apparent CV benefits.

4. By enhancing the insulin response to meals, DPP-4 inhibitors may also confer benefits when used in combination with basal insulin and metformin.

   DPP-4 inhibitors are also weight neutral.

5. The doctor and Eileen decide to combine metformin and the DPP-4 inhibitor with basal insulin.

6. Despite the benefits of using insulin to achieve glycaemic control, it carries a high risk of hypoglycaemia, which should be specifically avoided in those with CVD.

7. Eileen should receive sufficient education about insulin use to minimize risk.

References:


CVD, cardiovascular disease; DPP-4, Dipeptidyl-Peptidase 4; HbA$_{1c}$, glycosylated haemoglobin.
Option selected:
Begin basal insulin; discontinue existing therapies

- A priority for Eileen is to lower her HbA$_{1c}$ while also ensuring her safety
- Uncontrolled hyperglycaemia together with CVD place her at high risk for complications
- Therapies other than insulin are unlikely to provide sufficient benefit:$^1$
  - Eileen has long-standing diabetes and has not responded to a third oral agent: when triple oral therapy proves unsuccessful, the approach should be rapidly reconsidered
- There is no evidence to support the continued use of sulphonylureas with insulin
- However, metformin may minimize the weight gain associated with insulin therapy$^2$ and has apparent CV benefits$^3$
- By enhancing the insulin response to meals, DPP-4 inhibitors may also confer benefits when used in combination with basal insulin and metformin
  - DPP-4 inhibitors are also weight neutral$^{1,3}$
- The doctor and Eileen decide to combine metformin and the DPP-4 inhibitor with basal insulin
- Despite the benefits of using insulin to achieve glycaemic control, it carries a high risk of hypoglycaemia, which should be specifically avoided in those with CVD
- Eileen should receive sufficient education about insulin use to minimize risk$^1$


CVD, cardiovascular disease; DPP-4, Dipeptidyl peptidase-4; HbA$_{1c}$, glycosylated haemoglobin.
Setting a glycaemic target

- Prolonged periods of hyperglycaemia and established CVD place Eileen at high risk for vascular complications
- However, the need to achieve good glycaemic control must always be balanced against the need to ensure patient safety
- The doctor and Eileen re-address her glycaemic target

**Question**
What is an appropriate glycaemic target* for Eileen?

- <6.5%
- 6.5–7.0%
- 7.0–7.5%
- 7.5–8.0%

*Equivalent values: 6.5% = 48 mmol/mol; 7.0% = 53 mmol/mol; 7.5% = 58 mmol/mol; 8.0% = 64 mmol/mol.
An HbA₁c of <7.0% is recommended for most people with type 2 diabetes; however, treatment targets should always be tailored to the individual¹,²

Eileen is motivated, with good self-care capabilities and a strong support system

However, she has long-standing diabetes and CVD, placing her at high risk for complications and possible poor outcomes following hypoglycaemic events

Less stringent HbA₁c targets of 7.0–7.5% are recommended where safety is a concern²

*Equivalent values: 6.5% = 48 mmol/mol; 7.0% = 53 mmol/mol; 7.5% = 58 mmol/mol; 8.0% = 64 mmol/mol.

Reducing risk of hypoglycaemia

• For those using insulin, self monitoring of blood glucose (SMBG) is an essential component of diabetes management
• The doctor refers Eileen to a specialist diabetes nurse to learn about SMBG and how to adjust insulin in response to daily glucose fluctuations
• The nurse also teaches Eileen and her partner how to recognize and respond to hypoglycaemia

<table>
<thead>
<tr>
<th>Symptoms of hypoglycaemia¹</th>
<th>Neuroglycopenic</th>
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</thead>
<tbody>
<tr>
<td>Neurogenic (autonomic)</td>
<td></td>
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<tr>
<td>Trembling</td>
<td>Difficulty concentrating</td>
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<tr>
<td>Palpitations</td>
<td>Confusion</td>
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<tr>
<td>Sweating</td>
<td>Weakness</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Drowsiness</td>
</tr>
<tr>
<td>Hunger</td>
<td>Vision changes</td>
</tr>
<tr>
<td>Nausea</td>
<td>Difficulty speaking</td>
</tr>
<tr>
<td>Tingling</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
</tr>
</tbody>
</table>

3-month follow-up

- Eileen has made good progress, adjusting her basal insulin with the help and advice of the diabetes nurse.
- Her HbA$_1c$ is now below target levels.
- Eileen has not lost weight but has managed to maintain her weight despite beginning insulin therapy.
- She has been doing more walking with her partner to increase her physical activity levels.
- The doctor emphasizes the importance of lifestyle interventions for achieving good glycaemic control and minimizing cardiovascular risk.

FPG: 6.9 mmol/l (124 mg/dl)
HbA$_1c$: 6.8% (51 mmol/mol)
BP: 122/79 mmHg
BMI: 31.9 kg/m$^2$
10 Steps to get more people with type 2 diabetes to goal:

- Aim for an appropriate individualized glycaemic target, e.g. HbA$_{1c}$ 6.5–7% (48–53 mmol/mol) (or fasting/preprandial plasma glucose 110–130 mg/dl [6.0–7.2 mmol/l] where assessment of HbA$_{1c}$ is not possible) when safe and appropriate.
- Monitor HbA$_{1c}$ every 3 months in addition to appropriate glucose self-monitoring.
- Appropriately manage all cardiovascular risk factors.
- Refer all newly diagnosed patients to a unit specializing in diabetes care where possible.
- Address the underlying pathophysiology of diabetes, including the treatment of β-cell dysfunction and insulin resistance.
- Treat to achieve appropriate target HbA$_{1c}$ within 6 months of diagnosis.
- After 3 months, if patients are not at the desired target HbA$_{1c}$, consider combination therapy.
- Consider initiating combination therapy or insulin for patients with HbA$_{1c}$ ≥9% (≥75 mmol/mol).
- Use combinations of antihyperglycaemic agents with complementary mechanisms of action.
- Implement a multidisciplinary team approach that encourages patient self-management, education and self-care, with shared responsibilities to achieve goals.

HbA$_{1c}$, glycosylated haemoglobin.
