Therapeutics and Hypoglycaemia in the Elderly Patient with Diabetes

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Case Study 1 – Mr S

• 81 year old man
• Premorbid: ADL independent, community ambulant without aid
• Lives with daughter, main caregiver: domestic helper
• Medical hx
  – T2DM x 20 years, HbA1c 9.6%
  – Chronic kidney disease Stage 4, Creat 200, eGFR 26 ml/min
  – Hpt, Dyslipidaemia x 20 years
  – Alzheimer’s dementia – moderate, MMSE 18
  – Hypothyroidism
  – BPH
Medication List

- Thyroxine 100mcg OM
- Donepezil 5mg ON
- Escitalopram 10mg OM
- Terazosin 5mg ON
- Atorvastatin 40mg ON
- Vit B Complex 1/1 OM
- Losartan 100mg OM
- Nifedipine LA 30mg OM
- Linagliptin 5mg ON
- S/c Mixtard (30/70) 30 units OM, 20 units ON
Clinical Assessment

• No significant complaints
• Infrequent SMBG: 1x/week, usually ranging 7-16 mmol/l, occ 4.5 mmol/l
• BP 142/90 mmHg, no postural drop
• Injection sites: ok
• Feet: ok
Questions

• Is he having hypoglycaemia?
  – Risk factors for hypoglycaemia
  – Risks from hypoglycaemia
• Is his treatment for diabetes appropriate?
  – Risks a/w insulin therapy and type of insulin
• What is his HbA1c target?
What are the Risk Factors for Hypoglycaemia in this patient?

A  Age

B  Blood glucose lowering therapy – insulin/SU

C  Chronic kidney disease and Cognitive impairment (+/- Psychological problems)

D  Duration of DM
Does his suboptimal glycaemic control lessen his risk of hypoglycaemia?

**HbA1c and Risk of Hypoglycaemia**

- Intensive therapy is a/w increased risk of hypoglycaemia (DCCT study – 3 fold higher severe hypoglycemia in intensive group)
Glycaemic control and hypoglycaemia in T2DM

Intensive therapy contributes to an increased risk of hypoglycaemia by 2–3-fold, in advanced type 2 diabetes with cardiovascular disease.

ADVANCE, NEJM 2008; 358: 2560; ACCORD, NEJM 2008; 358: 2545; VADT, NEJM 2009; 360: 129; ORIGIN, NEJM 2012; 367;:319
This patient’s HbA1c is 9.6%...

• Does having a higher HBA1c protect against hypoglycaemia?

   NO!
**HbA1c and Risk of Severe Hypoglycaemia in T2DM**

- Self-reported hypoglycaemia was common (10.7% of cohort); insulin-treated patients (19%)
- Severe hypoglycaemia was common across all levels of glycaemic control
- Risk was higher in those with near-normal HbA1c or very poor glycaemic control
- Even after adjusting for age, duration of DM, type of treatment, the relationship of SH with HbA1c was still significant

Lipska, Diab Care 2014; 36:3535
Prevalence of severe hypoglycaemia in insulin-treated diabetes

Error bars = 95% confidence intervals

UK Hypoglycaemia Study Group, Diabetologia 2007; 50:1140-7
Is he having hypos?

Proof of Hypoglycaemia – SMBG (frequent) vs CGM

Sensor Data (mmol/L)

<table>
<thead>
<tr>
<th>Thu 31/05</th>
<th>Fri 01/06</th>
<th>Sat 02/06</th>
<th>Sun 03/06</th>
<th>Mon 04/06</th>
<th>Average</th>
</tr>
</thead>
</table>

Graph showing sensor data over a period with different colors for each day.
• Wide glucose fluctuations (highest BG 22.2 mM, lowest BG 2.3 mM)
• Average BG 11.6 mmol/l
What are the Risks from Hypoglycaemia?

**Brain**
Coma, seizures, cognitive impairment

**Cardiovascular**
Myocardial ischaemia, arrhythmias

**Musculoskeletal**
Falls, accidents, fractures, dislocations, driving accidents
Morbidity of Hypoglycaemia is affected by Age

Cardiovascular events

Coma, seizures

Falls, accidents, fractures
Diabetes and **Insulin Therapy** in Elderly are a/w Increased Risk of Hip Fractures

Incidence rate of hip fracture per 1000 person-years by diabetes status

![Graph showing incidence rate of hip fracture](chart.png)

Lipscombe et al, Diab Care 2007; 30: 835
Hypoglycaemia is a/w falls and fall-related fractures in people aged >65
Problems of treating diabetes in elderly people with insulin

- Social isolation – many live alone
- Dependency on nursing/social services is common
- Meals may be variable and inadequate
- May have practical difficulty (manual dexterity, vision) with self-administration of insulin, insulin therapy will necessitate BG testing
- Physical frailty, problems with vision and cognitive function (often progressive)
- Knowledge of symptoms and treatment of hypoglycaemia is limited
Which Insulin Therapy to choose in the Elderly? (1)

- Limited studies on the older elderly >75 years or with limited functional status (often excluded from trials)

- Type of insulin therapy
  - **Insulin analogues** seem to be safer, more physiologic pharmacologic profile, increased convenience and reduced risk of hypoglycaemia
  - **Basal insulin analogues** for convenience, may be able to achieve improved glycaemic control
  - Premixed insulins – added convenience, improved glycaemic control, but fixed regimes necessitate rigid oral intake

![Pharmacokinetic Profiles of Human Insulin and Insulin Analogues](image-url)
Which Insulin Therapy to choose in the Elderly? (2)

• Mode of administration
  – **Insulin pen devices** facilitate insulin dosing and patient independence

• Timing of administration
  • For basal insulin, **morning basal insulin** (instead of bedtime) may reduce risk of nocturnal hypoglycaemia
What should the glycaemic target be?

Patient characteristics that limit strict glycaemic control and influences choice of treatment

- Age
- Duration of diabetes
- Limited life expectancy
- Vulnerability to hypoglycaemia, impaired awareness of hypoglycaemia
- Advanced diabetic complications, especially renal function (impairment)
- Presence of co-morbidities and frailty
- Psychological and cognitive status
- (Unwilling to do BGM)

INDIVIDUALISED CARE
Cross-sectional analysis of 1288 older adults (≥65 years) with DM from NHANES 2001-2010

Health status categories: very complex/poor (difficulty ≥2 ADL or dialysis), intermediate/complex (difficulty with ≥iADL or ≥3 chronic conditions) or healthy

Examined tight glycaemic control (HbA1c <7%) and use of meds with high hypo risk (Insulin/SU)

Lipska et al, JAMA Int Med 2015; 175: 356
56% of those with very complex health and 63% with intermediate health had HbA1c <7%.

50-60% of those with HbA1c <7% were on insulin/ SU across all health categories.

Many older adults are overtreated with no change in HbA1c or prescription in 10 years of follow up.

Lipska et al, JAMA Int Med 2015; 175: 356
Glycaemic targets in frail elderly people (ADA and American Geriatrics Society)

• HbA1c 7- 7.5%
  – Very few co-morbidities
  – Preserved cognitive and physical function

• HbA1c 7.6-8.5%
  – Multiple chronic illnesses
  – Mild cognitive impairment
  – Risk of falls and hypoglycaemia

• HbA1c < 9.0%
  – End-stage chronic illnesses
  – Moderate to severe cognitive impairment
  – In long-term care

Kirkman et al, Diab Care 2012; 35: 2650; McLaren et al, BMJ 2013; 346:f2625
Summary & Recommendations for Case Study 1

• Elderly patient with CKD, dementia and depression, on Premix insulins, suboptimal HbA1c 9.6% but with hypoglycaemia

• Recommendations
  – Target HbA1c <9.0%
  – Pharmacotherapy – limited by above factors
    • DPP4 inhibitor, other oral agents with low risk of hypo
    • Insulin therapy:
      – Premix insulins – necessitate rigid oral intake
      – Basal insulin – Levemir/ Glargine
**CASE STUDY 2**

### 70-year-old man

#### Medical History

- Type 2 diabetes x 4 years
- Hypertension
- Dyslipidaemia
- Coronary artery disease
- Chronic obstructive airways disease
- Ex-smoker

#### Medication List

<table>
<thead>
<tr>
<th>Independent</th>
<th>Metformin 1g TDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stays with wife</td>
<td>Enalapril 10 mg BD</td>
</tr>
<tr>
<td></td>
<td>Amlodipine 10 mg OM</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 40 mg ON</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aspirin 100 mg OM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glibenclamide 10 mg BD</td>
</tr>
<tr>
<td>HbA1c 8.7%</td>
</tr>
<tr>
<td>Creatinine 144 μmol/L</td>
</tr>
<tr>
<td>eGFR 45 mL/min/BSA</td>
</tr>
</tbody>
</table>

#### Functional Status

- Independent
- Stays with wife
CASE STUDY 2

Found drowsy at bedtime. BGM “Lo” – reversed with dextrose. Recently unwell with fever and upper respiratory tract symptoms.

**Hospitalization**

**QUESTION 1**

Which of the following can contribute to his hypoglycaemia?

- A. Metformin
- B. Glibenclamide
- C. Renal failure
- D. Intercurrent illness

Maybe something else?
Drug-Drug Interactions

- Examples: clarithromycin, levofloxacin, co-trimoxazole, fluconazole
- Using cephalexin as a reference, a cross-sectional study showed elevated risk for hypoglycaemia for antibiotic use

<table>
<thead>
<tr>
<th>Drug</th>
<th>OR (Glipizide)</th>
<th>OR (Glyburide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotrimoxazole</td>
<td>3.14 (1.83-5.37)</td>
<td>2.68 (1.59-4.52)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>2.90 (1.69-4.98)</td>
<td>5.02 (3.35-7.54)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>2.09 (1.35-3.25)</td>
<td>2.83 (1.73-4.62)</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>2.53 (1.23-5.23)</td>
<td>2.20 (1.04-4.68)</td>
</tr>
</tbody>
</table>

Schelleman et al. Clin Pharmacol Ther 2010
CASE STUDY 2

Current Presentation

Well. No further hypoglycaemia.
SMBG: Pre-breakfast 8.2 – 11.4  Pre-dinner 9.0 – 14.7

QUESTION 2

Which of the following would you add to metformin?

A. Sulphonylurea
B. Meglitinide
C. Alpha-glucosidase inhibitor
D. Dipeptidyl peptidase-4 (DPP-4) inhibitor
E. Thiazolidinedione
F. Sodium-glucose cotransporter 2 (SLGT2) inhibitor
G. Glucagon-like peptide-1 (GLP-1) receptor agonist
H. Insulin
Metformin

Glycaemic Effects

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Cost</th>
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<tbody>
<tr>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>

Hypoglycaemic risk: Rare

Special Considerations

- First-line therapy
- Benefits include reduction of MACEs, improved survival
- Modest weight loss (or neutrality)
- Adverse effects: gastrointestinal intolerance, rarely lactic acidosis
- Always check renal function before and during use
- **Avoid** when eGFR is less than 30 mL/min/BSA
Sulphonylureas

Glycaemic Effects

- Efficacy: High
- Hypoglycaemic risk: Moderate
- Cost: Low

Special Considerations

- Avoid long-acting sulphonylureas: **glibenclamide**, (chlorpropamide)
- Significant secondary failure rate
- Weight gain
- Impairment of ischaemic preconditioning
- Be aware of situations predisposing to hypoglycaemia
### Alpha-Glucosidase Inhibitors

<table>
<thead>
<tr>
<th>Glycaemic Effects</th>
<th>Efficacy</th>
<th>Hypoglycaemic risk</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate</td>
<td>Rare</td>
<td>High</td>
</tr>
</tbody>
</table>

### Special Considerations

- Acarbose has minimal systemic absorption
- Weight neutral
- Frequent dosing at meals
- Concern for **gastrointestinal intolerance**
Dipeptidyl Peptidase-4 Inhibitors

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<th>Cost</th>
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<tbody>
<tr>
<td></td>
<td>Moderate</td>
<td>High</td>
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| Hypoglycaemic risk | Rare     |

**Special Considerations**

- Well-tolerated, once daily dosing regimen
- Weight neutral
- Probably safe from cardiovascular standpoint though saxagliptin was associated with an increase in hospitalization for heart failure
- **Dose reduction** required in renal insufficiency (except for linagliptin)
- Longer term data still required
### Sodium-Glucose Cotransporter 2 Inhibitors

<table>
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<th>Efficacy</th>
<th>Cost</th>
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<tbody>
<tr>
<td></td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td></td>
</tr>
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### Special Considerations

- Novel mechanism of action
- Well-tolerated, once daily dosing regimen
- Benefits include weight loss, blood pressure reduction
- More data required on use in older adults
- Concern for **genitourinary infections**, polyuria, **euglycaemic diabetic ketoacidosis** and possible fractures in elderly
<table>
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<th>Cost</th>
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<tr>
<td><strong>Efficacy</strong></td>
<td><strong>Hypoglycaemia</strong></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>GLP-1 Agonists</td>
<td>High</td>
<td>Very High</td>
</tr>
<tr>
<td>TZDs</td>
<td>High</td>
<td>High</td>
</tr>
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CASE STUDY 2

Well. No further hypoglycaemia.
SMBG: Pre-breakfast 8.2 – 11.4    Pre-dinner 9.0 – 14.7

QUESTION 2

Current Presentation

Which of the following would you add to metformin?

A. Sulphonylurea
B. Meglitinide
C. Alpha-glucosidase inhibitor
D. Dipeptidyl peptidase-4 (DPP-4) inhibitor
E. Thiazolidinedione
F. Sodium-glucose cotransporter 2 (SLGT2) inhibitor
G. Glucagon-like peptide-1 (GLP-1) receptor agonist
H. Insulin
### Medical History

- Type 2 diabetes x 20 years
  - Hypertension
  - Dyslipidaemia
  - Lumbar spinal stenosis
  - Osteoporosis with hip fracture
  - Parkinson disease
- Coronary artery disease
  - Heart Failure
  - Chronic kidney disease
  - Knee osteoarthritis
  - Stroke with vascular dementia
  - Postural hypotension

### Medication List

- **Aspirin 100 mg OD**
- **Amlodipine 10 mg OD**
- **Paracetamol 1g QDS**
- **Frusemide 40 mg BD**
- **Alendronate**
- **Lactulose**
- **Metformin 1g TDS**
- **Captopril 12.5 mg TDS**
- **Tramadol 50 mg TDS**
- **Propranolol 20 mg BD**
- **Calcium/Vitamin D Senna**
- **Glicazide 160 mg BD**
- **Clopidogrel 75 mg OD**
- **Madopar 62.5 mg QDS**
- **Mirtazapine 15 mg ON**
- **Sangobion**
- **Dulcolax**
**CASE STUDY 3**

**Medical History**

- Type 2 diabetes x 20 years
- Hypertension
- Dyslipidaemia
- Lumbar spinal stenosis
- Osteoporosis with hip fracture
- Parkinson disease
- Coronary artery disease
- Heart Failure
- Chronic kidney disease
- Knee osteoarthritis
- Stroke with vascular dementia
- Postural hypotension

**Functional Status**

- Frail, wheelchair bound
- Fussy with food

**Results**

- HbA1c 7.2%
- Creatinine 201 μmol/L
- eGFR 22 mL/min/BSA

**What is your approach?**
Polypharmacy

- Synergism, comorbidities, complications, cascade prescribing, lack of awareness/coordination
- Low adherence
- Escalating cost
- Drug-drug & drug-disease interactions
- Adverse drug reactions
- Geriatric syndromes
“Each capsule contains your medication, plus a treatment for each of its side effects.”
Tailor treatment goals for diabetes

Preventing disease complications vs. avoiding harm

(a) Assess hypoglycaemic risk

(b) Simplify treatment regimens & minimize polypharmacy

(c) Start slow and go slow

(d) Be aware of geriatric syndromes (which can change with time)

(e) Educate family and caregivers
**CASE STUDY 3**

**85-year-old woman**

### Medication List

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- Stop metformin and glicazide
- Review antihypertensives (once daily dosing)
- Revise analgesic agents
- Consider stopping non-essential medications (supplements)
- Consider drug holiday for alendronate
Comprehensive Geriatric Approach

Valencia WM, Florez H. Diabetes Obes Metab 2014
Take Home Messages

• T2DM is common in elderly population, often associated with frailty and multiple co-morbidities, progression of these comorbidities and cognitive impairment.

• Hypoglycaemia is more common than realised, regardless of HbA1c and may cause serious morbidity.

• Insulin therapy and SU therapy have high risk of hypoglycaemia.
  – For insulin therapy: consider type of insulin therapy, mode of administration and timing of therapy for convenience, more physiological profile and lower risk of hypoglycaemia.

• Strict glycaemic control may be inappropriate, targets should be individualised and may be less stringent than in younger people.
  – Changing HbA1c target (to less stringent) and simplification and changing medication regime is needed as the patient progresses on in life.