INSULIN INITIATION IN TYPE 2 DIABETES

A/Prof Mark Savage: Endocrinologist
Dr Jessica Triay: Endocrinologist
Dr Jessica Disler: Endocrinology advanced trainee
Karen Gray: Credentialled diabetes educator

Excellent Care. Every Person. Every Time.
Topics to be covered

• Identifying the requirement for insulin therapy
• Types of insulin available
• Addressing patient concerns
• Role of diabetes education
• Insulin starting dose and choice
• Titration and glycaemic targets
• Glycaemic variability and hypoglycaemia
Identifying Requirement For Insulin Therapy In Type 2 Diabetes

Dr Jessica Disler
Endocrinology Advanced Trainee
Type 1 vs Type 2 Diabetes

• Common end stage (dysglycaemia and the need for exogenous insulin)
• Insulin deficiency vs insulin resistance
• Residual endogenous insulin production and beta-cell mass

Eriksson (2011)
Pathogenesis of Type 2 Diabetes
Indications for Insulin in Type 2 Diabetes

- **Insulin deficiency**
  - Severe hyperglycaemia (extremely high HbA1c)
  - Catabolism
  - Ketonaemia or ketonuria
- Refractory to multiple agents and lifestyle interventions
  - Consider continuing some agents
- Individualise choice of therapy and target HbA1c
  - Age
  - Comorbidities
- [Latent autoimmune diabetes in adults (LADA)]
  - Consider endocrinology referral or discussion
Expected HbA1c Reduction
Side Effects of Insulin Therapy

- Weight gain
- Hypoglycaemia
  - Adrenergic
  - Neuroglycopena
  - Falls
- Injection site reactions
- Lipohypertrophy
  - Important to assess particularly in poor control
Types of Insulin

Dr Jessica Disler
Endocrinology Advanced Trainee
Endogenous Insulin

Normal (Non-diabetic) Blood Glucose and Insulin Levels over 24 Hours

- Blood Glucose
- Natural Insulin Secretion
Insulin Profiles

- **Insulin type**
  - Orange: Endogenous (ie non-diabetic)
  - Black: Rapid-acting (eg asprt, lispro)
  - Red: Analog pre-mixed
  - Yellow: Short-acting (ie regular)
  - Purple: Intermediate-acting (eg NPH)
  - Green: Long-acting (ie glargine, detemir)

**Relative insulin effects**

**Time (hours)**
Types of Exogenous Insulin

- Basal
- Prandial
- Mixed
Basal Insulin

**Long-Acting Insulin**
- Onset: 2-4 hours
- Duration: 24 hours

**Intermediate-Acting Insulin (NPH)**
- Onset: 0.5-1 hours
- Duration: 10-16 hours
Prandial Insulin

- Rapid-acting
- Short-acting
Mixed Insulin

- Intermediate + rapid acting
- Ultra-long acting + rapid acting
**BASAL (Lantus®)**

**LONG-ACTING INSULIN**

- **Onset:** 2-4 hours
- **Duration:** 24 hours

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**PRANDIAL**

**RAPID-ACTING INSULIN**

- **Onset:** ~5 minutes
- **Duration:** 4-5 hours

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**PREMIX**

**PREMIXED INSULIN (ANALOG)**

- **Onset:** 5-15 minutes
- **Duration:** 10-16 hours

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**INTERMEDIATE-ACTING INSULIN (NPH)**

- **Onset:** 0.5-1 hours
- **Duration:** 10-16 hours

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**SHORT-ACTING INSULIN (RHI)**

- **Onset:** 30 minutes
- **Duration:** Up to 6 hours
Key Points

• Insulin is indicated in insulin deficiency
  • Based on clinical parameters
• Individualise insulin choice to patient’s glycaemic profile and targets
Time to Start Insulin?
Role of the Diabetes Educator

Karen Gray
Team Leader, Diabetes Service
Addressing Patient Concerns

- Fear of needles
- Fear of addiction
- Fear of ‘hypo’s’
- “I might lose my licence…”
- Gaining weight
- Feeling like a failure
- Too much information to remember
- Will I have to be on it forever
- What if I do it wrong?
- My next door neighbour started insulin then went blind…
How can a diabetes educator help?

- Specialist in diabetes – credentialed with Australian Diabetes Educators Association
- Usually able to take more time with the patient
- Address patient fears and concerns
- Assess and teach appropriate delivery device
- Explain insulin action and why to give it at the appropriate times
- Talk about how to prevent the risks associated with insulin
- Feed back to referring GP
Where to find a diabetes educator..

- Public – Bendigo Region

  - **Bendigo Community Health Service Eaglehawk**
    - Clinics at Epsom, Queen St, Eaglehawk and Kangaroo Flat Centres
    - Small fee for service

  - **Bendigo Health Diabetes Educators**
    - Refer via Bendigo Health Referral Centre
    - Triage with BCHS
    - Fee for community health patients at BH
      - $14.90
      - $9.80 HCC
Referral to Credentialled Diabetes Educator

• Private Educators in Bendigo
  • GP Practice own educator
  • Local Private CDE’s
    • Fusion Allied Health – Deb Ludeman RN CDE
    • Happy Diabetes Health – Paul Skipper RN CDE
    • Simply Diabetes – Karen Gray RN CDE

• GP Management Plan and EPC minimum 2 visits required, depending on who is following up??
  • May be a GAP payment for patient education
What to put in the referral

- Diabetes type, date of diagnosis
- Comorbidities
- Context of insulin commencement
  - Insulin type, dose
  - Expectations for BG target
- Patient engagement
  - Are they ready for this change
- Plan for follow-up
  - Who and when
  - expectation for CDE engagement
- Consider dietitian referral
Insulin Prescription..

Commencement dose of insulin with choice of device

- Prescription given to patient – ready for first appointment
- Order appropriate device ie insulin pen or penfill cartridge if the patient is to have a non-disposable pen device
- Consider dexterity and/or vision concerns
**Initiation of Insulin Therapy and Stabilisation in an Ambulatory Setting**

To be completed by the referring medical officer.

<table>
<thead>
<tr>
<th>Referral to:</th>
<th>Credentialled Diabetes Educator</th>
<th>Date of Referral:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Details</td>
<td></td>
<td></td>
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<tr>
<td>Full Name:</td>
<td></td>
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<td>DOB:</td>
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<td>Contact Details:</td>
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<td>Referring Doctor:</td>
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<tr>
<td>Type 1</td>
<td>Type 2</td>
<td>Gestational</td>
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<td>Date of Diagnosis:</td>
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<td>Laboratory results:</td>
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<td>HbA1c:</td>
<td>BGL:</td>
<td>Urine Blood Ketones:</td>
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<td>Please attach other relevant test results.</td>
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<td></td>
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<tr>
<td>Current Diabetes Medications:</td>
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</table>

**Insulin Therapy Titration:**

Please tick appropriate section otherwise referral is invalid.

- [ ] The referring doctor wishes the diabetes educator to manage ongoing insulin dose adjustment.
- [ ] The referring doctor will manage ongoing insulin adjustment.

**Insulin Therapy Order:**

Type of Insulin: ______________________
Starting dosage: ______________________
Time and Regiment: ______________________

Target blood glucose range: Fasting (__________) Post Prandial (__________)
Size of incremental adjustments: ______________________

In Type 2 diabetes, is current oral therapy to be continued as "combination therapy"?
- [ ] Yes
  If yes, please state type of oral agent and dosage ______________________
- [ ] No

Expectations for progress reports: [ ] Weekly  [ ] Fortnightly
Method: [ ] Fax ______________________ or [ ] Letter

Other Comments: ______________________

Referring doctor name: ______________________
Referring doctor signature: ______________________
Non-Disposable Pens

• For penfill cartridges
• Advantages
  • Less space taken up for storage
  • Less ‘disposable plastic’
  • Can be smoother delivery
• Each insulin company has a version of non-disposable pen
• Can be supplied at no cost by diabetes educators
Non-Disposable Pens – Half Unit

• Delivers half unit increments
• Not usually needed with type 2 patients
  (great for children)
Education

• Take time
  • Patient’s own pace
  • Barriers addressed
  • Careful explanation

• Let them try – first injection or ‘dry run’ in clinic

• Devices – pens, syringes
  • Pre-loaded and disposable
  • Non-disposable

• Pen needle length
  • 4mm, 6mm
  • Single use
  • Injection angle 90°
First Visit

- Explain benefits of insulin
- Check NDSS
- Show injection technique
- First injection supervised
- Discuss hypoglycaemia – recognition and how to manage it
- Discuss potential weight gain and how to minimise
- Daily management – injections, needle changes, SMBG, targets, titration, when and who to call
- Sharps disposal
- Provide instruction sheet to follow for injection at home
- Plan follow up visit
- Who to contact for concerns
NDSS Requirement

- NDSS upgrade to insulin – medication change form
  - Free pen-needles or syringes
  - Patient eligible for ongoing glucose strips
  - GP or CDE sign off
Follow up visit..

• Listen to concerns/issues
• Review the glucose record book
• Review injection technique
• Begin/continue titration to target BG
Injection sites – rotate!

- Rotation of injection sites important
- Check for lipohypertrophy each visit
  - Occurs if using same site continually
Hypoglycaemia

- **Rule of 15**
  - Low BGL treat with 15 gm High Gl carb
  - Check BG again in 15 mins
  - If still < 4.0 repeat 15 gm high Gl carb
  - When > 4.0 give low Gl carb
  - Advise to carry glucose
  - Care with driving

- Glucagen Hypokit – not required for type 2
  - Expensive
  - Goes out of date
  - May not be very effective in type 2 DM
Extra Information for Patients

• Sharps containers – available free from council on a replacement system

• VicRoads requirements when on insulin
  Over “5” to drive campaign.

• Hypo management

• Advice on how to manage if special situations such as surgery, fasting or steroids
  Ongoing reviews and support
Resources


Choosing insulin starting dose, What to prescribe, & Early titration

Primary Care Insulin Initiation
Dr Jessica Triay
Look at the blood sugar pattern. Which insulin best fits with the profile?

• Prior to choosing insulin regimen, if possible, 3 days of intensive glucose monitoring for daily profile.

• Pre- and 2 hours post- largest meal of the day

• Consider how do these compare with targets:
  • Fasting and pre-prandial 6–8 mmol/L
  • 2 hour post-prandial 6–10 mmol/L (post meal rise < 2.5 mmol/L)
Look at the blood sugar pattern. Which insulin choice matches the profile?
Concurrent OHAs

• Generally continue to reduce insulin requirements, flatten glucose profile, and reduce hypoglycaemia unless:
  
  • Side effects
  • No response to OHA
  • Significant treatment burden
## Fasting hyperglycaemia

<table>
<thead>
<tr>
<th></th>
<th>Before breakfast</th>
<th>After breakfast</th>
<th>Before lunch</th>
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<th>Before dinner</th>
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<tbody>
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<td>11.2</td>
<td>12.1</td>
<td>8.9</td>
<td>9.0</td>
<td>9.3</td>
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<td>9.7</td>
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</tbody>
</table>

- Once daily basal insulin
- Before bed is simplest regimen
Post-prandial hyperglycaemia

<table>
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<th>After lunch</th>
<th>Before dinner</th>
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<tbody>
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<td>14.7</td>
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<tr>
<td>11.2</td>
<td>12.1</td>
<td>8.9</td>
<td>9.0</td>
<td>9.3</td>
<td>15.9</td>
</tr>
</tbody>
</table>

- Often have hyperglycaemia at other times
- Options basal-bolus vs premixed insulin
## Basal-Bolus vs. Mixed/Biphasic insulin

<table>
<thead>
<tr>
<th></th>
<th>Basal Bolus</th>
<th>Mixed Biphasic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly variable carbohydrate intake</td>
<td>✔️</td>
<td>❌</td>
</tr>
<tr>
<td>Variable daily routine</td>
<td>✔️</td>
<td>❌</td>
</tr>
<tr>
<td>Strict control needed</td>
<td>✔️</td>
<td>❌</td>
</tr>
<tr>
<td>Concerns about weight gain</td>
<td>✔️</td>
<td>❌</td>
</tr>
<tr>
<td>Concerns about compliance/convenience</td>
<td>❌</td>
<td>✔️</td>
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</tbody>
</table>
Starting dose, timing and testing

• **Start low and go slow!**
• Allow time to become confident with insulin administration and safety
  • Basal insulin 8–10 units
  • Mixed insulin 8–10 units once daily with largest meal (dinner)
Weight based starting dose

- Useful if need to gain more rapid control, or likely to require much higher insulin doses. Needs closer observation.

- Start as 0.2 units/kg then titrate
- e.g. 100kg patient, commence with 20 units
Titration

- Review at least weekly after initiation
- Titrate to a specific glucose target level (chosen to be appropriate for insulin chosen)

<table>
<thead>
<tr>
<th>Glucose Level</th>
<th>Action</th>
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<tbody>
<tr>
<td>&gt;10</td>
<td>increase by 4 units</td>
</tr>
<tr>
<td>8-10</td>
<td>increase by 2 units</td>
</tr>
<tr>
<td>7-7.9</td>
<td>Wait or increase 2 units</td>
</tr>
<tr>
<td>6-6.9</td>
<td>No change</td>
</tr>
<tr>
<td>4-5.9</td>
<td>Reduce by 2 units</td>
</tr>
<tr>
<td>&lt;4 or Hypoglycaemia symptoms</td>
<td>Reduce by 4 units</td>
</tr>
</tbody>
</table>
Adjust titration according to response observed

- Good response - may wish to reduce sizes of insulin increments
- Limited response - may wish to increase size of insulin increments
- Some patients may be taught how to self-titrate according to algorithm to safe cut offs
Example Case
Robert 67 years old, BMI 41, normal renal function, retired truck driver, HbA1c 10% (86 mmol/mol)

- metformin 1000 mg BD, gliclazide MR 120 mg, empagliflozin 25 mg, linagliptin 5 mg
- Chose insulin type and starting dose

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<th>After breakfast</th>
<th>Before lunch</th>
<th>After lunch</th>
<th>Before dinner</th>
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<tbody>
<tr>
<td>Before breakfast 10.3</td>
<td>11.4</td>
<td>11.0</td>
<td>11.3</td>
<td>10.1</td>
<td>10.2</td>
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<tr>
<td>After breakfast 11.2</td>
<td>12.1</td>
<td>12.2</td>
<td>13.7</td>
<td>12.3</td>
<td>13.9</td>
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</tbody>
</table>
• Long acting insulin 10 units nocte commenced 4 days ago
• What now?

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<th>Before breakfast</th>
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<td>11.2</td>
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<td>13.7</td>
<td>12.3</td>
<td>13.9</td>
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</tbody>
</table>
Long acting insulin increased to 14 units 4 days ago. What now?

- Review technique and administration
- Change titration regimen to allow for larger increments
- Direct to increase every 3–4 days by 2 units if fasting glucose > 8 mmol/L and arrange follow up for review

<table>
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<tr>
<th>Before breakfast</th>
<th>After breakfast</th>
<th>Before lunch</th>
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<th>Before dinner</th>
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<tbody>
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<td>10.3</td>
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<td>11.2</td>
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<td>12.2</td>
<td>13.7</td>
<td>12.3</td>
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</tbody>
</table>
• Long acting insulin is now 32 units at bed time
• Continues on metformin 1000 mg BD, gliclazide MR 120 mg, Empagliflozin 25 mg, sitagliptin 100 mg
• Has seen a dietitian, walking more in the day

<table>
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<th>Before lunch</th>
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<td>7.9</td>
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<td>7.7</td>
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</table>
Example Case
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<tr>
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<th>Before lunch</th>
<th>After lunch</th>
<th>Before dinner</th>
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</thead>
<tbody>
<tr>
<td>Sue 54 F, BMI 33, normal renal function</td>
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<tr>
<td>Secretary part time, looks after grandchildren two days a week</td>
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<tr>
<td>Metformin 1000 mg BD, dapaglifloxin 10 mg, saxagliptin 5 mg</td>
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<tr>
<td>What insulin choice? What starting dose?</td>
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</table>
• Sue opted for 25% insulin lispro and 75% insulin lispro protamine sulfate suspension 8 units commenced with evening meal 3 days ago

• What do you recommend now?

<table>
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<tr>
<th></th>
<th>Before Breakfast</th>
<th>After Breakfast</th>
<th>Before Lunch</th>
<th>After Lunch</th>
<th>Before Dinner</th>
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<tbody>
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</table>
- 25% insulin lispro and 75% insulin lispro protamine sulfate suspension now up to 12 units with evening meal and 8 units breakfast on work days only
- What do you recommend now?

<table>
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<th>Before breakfast</th>
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<th>Before lunch</th>
<th>After lunch</th>
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<td>8.1</td>
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</table>
- 25% insulin lispro and 75% insulin lispro protamine sulfate suspension 18 units with evening meal 12 units breakfast on work days only
- Continues on metformin 1000 mg BD, dapagliflozin 10 mg, linagliptin 5 mg
Example Case

Listed for total hip replacement next month but HbA1c 11.4%. Diabetes control has deteriorated significantly over last 8 months due to reduced mobility.

What insulin choice? What starting dose?
- Long acting insulin 8 units before bed
- Rapid acting insulin 5 units before evening meal

<table>
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<th>Before lunch</th>
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<td>10.3</td>
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<td>Blood glucose</td>
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<td>9.8</td>
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</table>

Excellent Care. Every Person. Every Time.
- Long acting insulin titrated up to 28 units before bed
- Rapid acting insulin 8, 6, 12 with meals

<table>
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<td>After breakfast</td>
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<td>6.7</td>
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Safely escalating doses, recognising when hypoglycaemia is a problem & glucose variability

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Overview/Introduction

• This talk will focus on T2DM
• CHO counting, pump management and Dose Adjustment For Normal Eating (DAFNE)/Flexit etc. for type 1 management is tricky
  • Should be done by very interested and focussed Primary Care Physicians
  • Or specialists
• Some type 1 folk *not* on intensive regimens will follow principles to be discussed – because not numerically literate or lifestyle issues dictate
Take Home #1

• #1 HbA1c is not always related to blood glucose – even in those with normal haemoglobin
HbA1c to Mean Plasma Glucose
What are the BGL Targets in T2DM? Take home message #2

• Depends……..
• There is a relationship in early and uncomplicated T2DM between glycaemic control and CVD
• So, early uncomplicated T2DM aim HbA1c < 53 mmol/mol or 7%
What are the BGL Targets in T2DM? Take home message #2

• For the elderly and those with established complications such as CVD; neuropathy and renal disease
  • Treat blood pressure
  • Treat lipids
  • Then treat glucose
• Avoid hypos in this group – **evidence of probable harm if too aggressive**
  **ACCORD study discontinued due to higher death rate**
• HbA1c **not** required to be < 53 mmol/mol or 7%, for most of these therefore reasonable to be < 64 mmol/mol (8%)
RACGP T2DM Targets

• So…….
• HbA1c targets to be individualised (RACGP)
• Where safe aim for <53 mmol/mol (< 7%)
Hypoglycaemia

• Hypoglycaemia
  • “Four is the Floor”
  • Classic symptoms are adrenergic
  • If loss of symptoms then neurogenic take over – confusion, behavioural, coma
  • Chronically low BGLs leads to poor or absent warnings
  • Best predictor of serious hypoglycaemic risk is previous severe hypoglycaemia
Hypoglycaemia Prevention

• Acknowledge and address the problem in every person treated with insulin or an insulin secretagogue at every consultation
• What frequency does low blood glucose occur—explainable or unexplainable?
• Review SMBG records/examine meter
• At what level does the person detect/develop symptoms of hypoglycemia?
Hypo Prevention 2

• Do others ever detect hypoglycemia before the person with diabetes?
• Risk factors that result in relative or absolute hyperinsulinemia – CHO, exercise etc.
• Timing/type and dose of insulin or insulin secretagogue – MDI increases risk in T2DM vs basal insulin
• Situations in which exogenous or endogenous glucose delivery is decreased – gastroparesis or liver cirrhosis
• Renal failure (increases insulin half life)
Reminder – sub cut insulin is a really bad treatment for diabetes
Escalation of Insulin Doses

• Depends on insulin type
  • Rapid acting analogues can be increased every day or two - dependent on response to post prandial 2 hour levels
  • Fixed Mix better to increase after a few days of blood glucose results to ascertain a pattern
  • Adjust dose before abnormal levels
  • Long acting insulin and insulin analogues increase every few days
Increasing Basal Insulin

- Patients can alter their own insulin
- BB glucose is best indicator in most patients
- Advise to increase intermediate and long acting insulin by 2 units every 3 days
  - Stop increase when BB glucose < 7 mmol/L
  - Stop increase if hypos occur
Increasing Pre Meal Rapid Acting Insulin

• To be taken 15-20 minutes before – ideally
• The 2 hour post prandial blood glucose level best indicator, aim 4-10 mmol/L
Fixed Mix most challenging

• A biphasic suspension of 30% soluble insulin aspart (rapid-acting human insulin analogue) and 70% protamine-crystallised insulin aspart (intermediate-acting human insulin analogue 24 units am and 16 evening

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• Suggestions?
• Dietitian for CHO assessment and drop evening dose (hypos); maybe increase am dose too, but BD OK…..
• Maybe Basal - Bolus needed
Lantus, Toujeo and Ryzodeg

• Evidence for fewer hypos overnight in patients in randomised trials with good HbA1c levels (about 53 mmol/mol or 7%)
• Most real life patients have poorer control so hypos less of an issue
• Much more cost effective to engage Diabetes Educator rather than spending tax-dollars on expensive sexy insulins.
• NICE in UK recommend once or twice daily Protaphane (NPH) as the starting insulin
• Best indicator of insulin trial outcomes is the Trial Sponsor
Glucose variability

• Glycaemic variability (GV), refers to swings in blood glucose levels
• Has a broader meaning because it alludes to blood glucose oscillations, including hypoglycaemic periods and postprandial increases, as well as blood glucose fluctuations that occur at the same time on different days – despite there being little difference in behaviour, CHO intake or exercise.
Variability

• Impossible to measure accurately without CGM/Flash monitoring; but frequent HBGM results can provide an insight.

• Time in target (agreed for now to be 4–10 mmol/L) of 70% suggests less variability.
If too random.....
Summary

• More results from the patient the easier it is to adjust
• Take one’s time
• Be methodical
• If you want 3 opinions ask 2 Endocrinologists!