Type 2 diabetes is a progressive disease: its treatment – the current status

Associate Professor Jonathan Shaw
• Why is type 2 diabetes so hard to treat?

• How to choose the right glucose-lowering drug?
Why is type 2 diabetes so hard to treat?

• Multiple pathophysiological abnormalities
Multiple causes of T2 diabetes

- Decreased Insulin Secretion
- Increased Lipolysis
- Decreased Incretin Effect
- Increased Glucagon Secretion
- Increased HGP
- Decreased Glucose Uptake
- Neurotransmitter Dysfunction

HYPERGLYCEMIA

Courtesy of Ralph de Fronzo
Why is type 2 diabetes so hard to treat?

• Multiple pathophysiological abnormalities
  – Hard to know which is important in each patient
  – Multiple abnormalities may require multiple drugs
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- Disease is progressive
β-Cell Function Declines Regardless of Intervention in T2DM

*β-cell function measured by HOMA

HbA$_{1c}$ cross-sectional, median values

- Conventional
- Intensive

6.2% upper limit of normal range
HbA$_{1c}$

overweight patients

cohort, median values

Years from randomisation

ukpds
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- Disease is progressive
- Lifestyle change is hard
- Drug compliance is often poor
  - 43% of patients discontinue statins after 6 months
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- Disease is progressive
- Lifestyle change is hard
- Drug compliance is often poor
- Drugs are not very potent
Successful management will often require

- Multidisciplinary team addressing
  - Pathophysiology
  - Education
  - Social setting of the disease within a patient’s life
  - Community beliefs about disease
- Multiple drugs
Glucose-lowering drugs

- Metformin
- Sulphonylureas
- Glitazones
- Acarbose
- DPP4 inhibitors
- GLP1 agonists
- Insulin – long-acting, mixed, short-acting
How to select therapy

• Metformin remains the 1st choice
  – Evidence for micro and macrovascular benefit
  – No hypos; no weight gain

• Sulphonylureas are 2nd choice in many guidelines
  – Evidence for micro and macrovascular benefit
  – But – hypos and weight gain
What is 3\textsuperscript{rd} line therapy???

- **Insulin**
  - Most will need it eventually
  - Evidence for micro and macrovascular benefit
  - Hypos and weight gain

- **Actos**
  - Treats insulin resistance
  - Possible macrovascular benefit; no hypos
  - Weight gain, fractures
What is 3rd line therapy???

- **GLP1 analogues**
  - Weight loss; no hypos
  - Injections
  - No long-term outcome data yet

- **DPP4i**
  - Weight neutral; no hypos
  - Oral
  - No long-term outcome data yet
Incretins and the cardiovascular system

DPP4i and CVD risk

- 53 trials
- Mean duration ~8 months
- >30,000 patients
- DPP4i vs comparator
- 257 major CV events
- Risk reduction 31%

Odds ratio: 0.69 (0.53-0.90)
Principles for best management

• Start with drugs that have long-term outcome data
• Expect to use multiple agents
• Avoid hypos in those with multiple comorbidities
• Assess compliance and reasons for non-compliance
• Glucose-lowering is only 1 part of the puzzle
“I want you to quit smoking and drinking, cut back on salt, ease up on red meat and sweets, don’t snack between meals, exercise more and just enjoy life.”