Agenda

- Metabolic Syndrome and “Prediabetes”
- Diabetes
- Hyperprolactinaemia
- Thyroid disease
"It's time we face reality, my friends. ... We're not exactly rocket scientists."
“Prediabetes”

- Better termed “intermediate hyperglycaemia” or “dysglycaemia”

### Table 1: Diagnostic criteria for prediabetes

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<tbody>
<tr>
<td><strong>Venous plasma glucose</strong></td>
<td></td>
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<tr>
<td></td>
<td>7.1-8.2 mmol/L (postload)</td>
<td>&lt;8.0 mmol/L (fasting), ≥8.0 mmol/L and &lt;11.0 mmol/L (2 h postload)</td>
<td>&lt;7.8 mmol/L (fasting), ≥7.8 mmol/L and &lt;11.1 mmol/L (2 h postload)</td>
<td>IGT: &lt;7.0 mmol/L (fasting), ≥7.8 mmol/L and &lt;11.1 mmol/L (2 h postload); IFG: ≥6.1 mmol/L and &lt;7.0 mmol/L (fasting), &lt;7.8 mmol/L (2 h postload, if measured*)</td>
<td>IGT: &lt;7.0 mmol/L (fasting), ≥7.8 mmol/L and &lt;11.1 mmol/L (2 h postload); IFG: ≥6.1-6.9 mmol/L (fasting)</td>
<td>IGT: &lt;7.0 mmol/L (fasting), ≥7.8-11.0 mmol/L (2 h postload); IFG: ≥5.6-6.9 mmol/L (fasting)†; HbA&lt;sub&gt;1c&lt;/sub&gt;: 5.7-6.4%</td>
<td></td>
</tr>
</tbody>
</table>

One abnormal test result defines prediabetes; no repeat testing is required. IGT=impaired glucose tolerance. IFG=impaired fasting glucose. ADA=American Diabetes Association. HbA<sub>1c</sub>=glycated haemoglobin. *Measurement is recommended to exclude diabetes or IGT + 7 h postload glucose measurement not recommended.
Prediabetes

- Variable definitions, and prevalence very sensitive to definitional changes
- Heterogeneous, with minority overlap between IFG and IGT (25%)
  - IFG: hepatic insulin resistance, impaired early insulin response
  - IGT: muscle insulin resistance, impaired early and late-phase insulin secretion
- Now largely based on HBA1c...but we don’t know if this is the same population as trials based on IFG
“Natural History” of Prediabetes

Secular changes

• From 1980-2008 fasting glucose has risen by 0.1mmol/l

• Small effect in large population leads to:
  – Potential large burden in disease
  – Certain significant increase in “those at risk”
Total diabetes and pre-diabetes age-specific rates for men

2008/09 New Zealand Adult Nutrition Survey
Total diabetes and pre-diabetes age-specific rates for women

Prevalence (%) for age groups:
- Diabetes
- Prediabetes

Age groups (years):
15-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75+

Prevalence (%):
- Diabetes: 0, 5, 10, 15, 20, 25, 30, 35, 40, 45
- Prediabetes: 0, 5, 10, 15, 20, 25, 30, 35, 40, 45
Pre-diabetes prevalence (Auckland)

Prevalence of prediabetes in the Auckland metro region in 2013 (out of those who had HbA1c, GTT, fasting glucose) excluding people with diabetes.
Pre-diabetes + diabetes prevalence

Prevalence of prediabetes or diabetes in the Auckland metro region in 2013
(out of those who had HbA1c, GTT, fasting glucose)
“Natural History”

Progression from Prediabetes to Diabetes:

• 5-10%/yr
  – Isolated IFG 6-9%
  – Isolated IGT 4-6%
  – Combined 15-19%

• Estimated lifetime risk 70% (ADA Expert panel)

• More recent work in Auckland (2014-2017, era of systematic screening) suggests approx 1% per annum.
“Natural History”

Regression from Prediabetes to normoglycaemia:
• 19% DPP control group (at 10 yr FU study)
• 55-80% IFG Ely Study (UK, 10 year FU)

Progression to diabetes may not be better predicted by “prediabetes” state than other risk approaches
Interventions

In trial settings, in enrolled participants confirmed to be in “prediabetes” range (i.e. 2 tests):

• Lifestyle interventions reduce prediabetes to diabetes conversion (over 3-5 years) by 50%
  – Better than metformin
  – No additivity with metformin (DPP)
  – No additivity with pioglitazone (Indian DPP-2)

• Reduced rates of “conversion” appear robust on longer term follow-up
Issues with Prediabetes “intervention” in real life

• Identifying target population
• Real-world implementation
• “medicalising” a “state” in absence of hard outcome/endpoint data
• The size of the problem
How will we cope?
Metabolic Syndrome

Metabolic syndrome is the name for a group of risk factors that raises your risk for heart disease and other health problems, such as diabetes and stroke.

– Dysmetabolic syndrome
– Hypertriglyceridemic waist
– Insulin resistance syndrome
– Obesity syndrome
– Syndrome X
Metabolic Syndrome and Psychiatry

• 2/3 those with BPAD or schizoeffective disorder
• ½ with Scizophrenia
• More in woman than men.
Problems with “Metabolic syndrome”

• Lack of consensus on definition
• Validity for differing ethnicities
• No known treatment specific to the cluster
• “Binomial” approach to components
• Lack of age and gender and past history (eg of IHD) in the assessment of risk
• Doesn’t have clinical utility (ADA and EASD)
"I think you should be more explicit here in step two."
Diabetes, *the Tsunami*
Diabetes prevalence by ethnicity in CM Health

CM Health age specific diabetes prevalence by ethnicity in 2017

- Maori
- Pacific
- Indian
- Chinese
- Other Asian
- European/Other
% of people with diabetes who had a last hbA1c ≥75 mmol/mol by age and ethnicity

- Maori
- Pacific
- Indian
- Chinese
- Other Asian
- European/Other
% of people with diabetes in 2017 who had a last hbA1c ≥75 mmo/mol by age and NZDep 2013 (MB from PHO 2018Q1)
Diabetes and Mental Illness

• Mental health problems and Diabetes are common and increasing
  – *Causes are complex*
  – *More common in most deprived*
  – *People with diabetes have greater risks of mental illness (2 fold, mainly associated with depression)* and
  – *People with mental illness have increased risk of diabetes*
  – *Each condition is associated with substantive comorbidity and premature mortality*
  – *Medications used for mental illness may increase risk of diabetes*
Antipsychotic Medication and Diabetes

possible mechanisms

• Impairing insulin secretion
  — relative or absolute insulin lack

• Impairing action of insulin
  — “insulin resistance”

• there is little evidence of decreased insulin release in all but those found to have Type I DM (? Co-existing not causally related)
Antipsychotic Medication and Weight Gain

Described since 1950’s

- 50% of patients on chronic treatment
- commonest causes for non-compliance and/or discontinuation
- Maximal effect in 1st 3–4/12, but tends to progress
- Weight gain not restricted to those of low BMI
- Concomitant treatment with mood stabilisers and antidepressants is associated with increased weight gain
Figure 5. Antipsychotics and Weight Gain: Short-Term (10-weeks) Treatment

Reprinted with permission from Allison et al. 

\(^a\)
Figure 2. Mean Change in Weight During Clinical Studies of Olanzapine
Randomised db

Am J Psychiatry 2001; 158:765–774
Obesity Trends* Among U.S. Adults

BRFSS, 1985

(*BMI ≥ 30, or ~ 30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

BRFSS, 1986

(*BMI ≥30, or ~30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

BRFSS, 1987

(*BMI ≥ 30, or ~ 30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

*BRFSS, 1988

(*BMI ≥30, or ~30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

**BRFSS, 1989**

(*BMI ≥ 30, or ~30 lbs overweight for 5’4” woman*)

Obesity Trends* Among U.S. Adults

BRFSS, 1990

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Obesity Trends* Among U.S. Adults

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**BRFSS. 1992**

(*BMI ≥30, or ~30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

BRFSS, 1993

(*BMI ≥30, or ∼30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

BRFSS. 1994

(*BMI ≥ 30, or ~30 lbs overweight for 5'4" woman)

Obesity Trends* Among U.S. Adults

BRFSS. 1995

(*BMI ≥ 30, or ~30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

BRFSS. 1996

(*BMI ≥ 30, or ~ 30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

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Obesity Trends* Among U.S. Adults

**BRFSS, 1999**

(*BMI ≥ 30, or ~30 lbs overweight for 5'4" woman*)

Obesity Trends* Among U.S. Adults
BRFSS. 2000
(*BMI ≥30, or ~30 lbs overweight for 5'4" woman)

Obesity Trends* Among U.S. Adults

BRFSS. 2001

(*BMI ≥ 30, or ∼ 30 lbs overweight for 5’4” woman)

Recommendations

- Consider risks when commencing antipsychotic
- Patient, family and caregiver education
- Baseline screening
- Regular monitoring
- Referral to specialised services, when appropriate

*Consensus Development Conference on Antipsychotic Drugs And Obesity and Diabetes

*J Clin Psych 65:2; 267-72 Feb 2004*
Management of Type 2 DM

• Multifactorial
  – Glucose
  – BP
  – CVD risk
  – Reno-protection
• Lifestyle
• Pharmacotherapy
• Surgery
• Palliation
Pathophysiologic Approach to Treatment of T2DM

Impaired Insulin Secretion

TZDs
GLP-1 analogues
DPP-4 inhibitors
Sulfonylureas
Metformin
Thiazolidinediones

Increased Hepatic Glucose Production

Hyperglycemia
Metformin

Decreased Glucose Uptake

Association between mean HbA1c and complications: UKPDS

Each 1% fall in HbA1c represents a decrease in risk of...

- Lower extremity amputation or fatal peripheral vascular disease*: 43%*
- Microvascular disease*: 37%*
- Cataract extraction*: 19%*
- Heart failure*: 16%*
- Myocardial infarction*: 14%*
- Stroke*: 12%*

† Single endpoint
# Aggregate endpoint
* p<0.05

Adapted from Stratton IM et al. on behalf of the UK Prospective Diabetes Study Group. BMJ 2000; 321:405–412.
RENAAL Patients Reaching the Primary Composite Endpoint*

Risk reduction = 16%
P = 0.02

In combination with open-label diuretic, calcium channel blocker, beta-blocker, alpha-blocker, and/or centrally acting agent

*Doubling of serum creatinine, end stage renal disease, and/or death

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Multirisk factor management: Steno-2 Post Trial: Any CVD events

Log-rank P=0.0002

Numbers at risk
Conventional 80 70 60 46 38 29 25 14
Intensive 80 72 65 61 56 50 47 31

Gaede et al. NEJM 2008
Steno-2 Post Trial: Mortality of any cause

Log-rank P=0.015

Cumulative incidence of death (%)

Years of follow-up

Conventional Intensive

Numbers at risk

Conventional 80 80 77 69 63 51 43 30
Intensive 80 78 75 72 65 62 57 39

Gaede et al. NEJM 2008
### Steno 2 Study

**Number of microalbuminuric patients with type 2 diabetes needed to treat for 13 years to prevent one...**

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>5 patients</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>8 patients</td>
</tr>
<tr>
<td>Major cardiovascular event</td>
<td>3 patients</td>
</tr>
<tr>
<td>Progression to nephropathy</td>
<td>5 patients</td>
</tr>
<tr>
<td>Dialysis</td>
<td>16 patients</td>
</tr>
<tr>
<td>Laser treatment</td>
<td>7 patients</td>
</tr>
<tr>
<td>Death</td>
<td>5 patients</td>
</tr>
</tbody>
</table>

(from Gaede et al 2008 Steno 2, 13 year study)
Diabetes problems

- The disease progresses
- Complications accrue
- Glycaemia is dynamic, and optimising glycaemic management requires expertise
- Complications and (increasing) treatment effects can get in way of realising the improvements
- Latency for results

After median 8.5 years post-trial follow-up

**Aggregate Endpoint**

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th>1997</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td>RRR: 12%</td>
<td>P: 0.029</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>RRR: 25%</td>
<td>P: 0.0099</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>RRR: 16%</td>
<td>P: 0.052</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>RRR: 6%</td>
<td>P: 0.44</td>
</tr>
</tbody>
</table>

Steno-2 mortality

UKPDS PTFU mean 18.5 years since diagnosis
The Era of the Guideline

For a very brief period, medieval scientists were known to have dabbled in the merits of cardboard armor.
Management of glycaemic control (NZ)

If above target (HbA$_1c$ 50-55 mmol/mol [6.7 – 7.2%] or as individually agreed)

Lifestyle modification
- Food, physical activity and behavioural strategies

If measured HbA$_1c$ does not meet or closely approach agreed target within 3 months, or if patient is symptomatic, drug therapy should be considered

First line drug therapy
- Metformin
  - Gastrointestinal tolerance may be improved by gradual introduction
  - Stop if eGFR <30 ml/min/1.73m$^2$
- Sulphonylurea
  - If metformin not tolerated or contraindicated
  - Educate the person on the possibility of hypoglycaemia

If above target >3 months

Second line drug therapy
- Sulphonylurea
  - Review medication adherence and dose optimisation

If above target >3 months

Third line drug therapy
- Thiazolidinedione (pioglitazone)$^2, 3$
  - If no congestive heart failure
  - If at significant risk of hypoglycaemia
  - Consider increased risk of fracture in women
- Insulin$^4$
  - Review medication adherence and dose optimisation

Guidance on the Management of Type 2 Diabetes 2011; available online at www.nzgg.org.nz
### Figure 4. Australian diabetes algorithm and clinical medication table

**First line:** Metformin is the usual first-line therapy unless contraindicated or not tolerated

- Metformin
- Sulphonylureas (SU)
- Glipizide
- Dipeptidyl peptidase-4 inhibitors (DPP-4i)
- Sodium glucose co-transporter 2 inhibitors (SGLT2i)
- Insulin
- Acarbose
- Thiazolidinediones (TZD)

If glycated haemoglobin (HbA1c) target not achieved in three months:

- check and review current therapies, stop any that fail to improve glycaemic control
- check patient’s understanding and self-management
- review use of therapies
- exclude other comorbidities/therapies impacting on glycaemic control

**Second line:** If metformin was not used first line, add it now, if not contraindicated

SU are the usual initial agent to add to metformin. If SU are contraindicated or not tolerated, another agent may be used:

- SU
- DPP-4i
- SGLT2i
- Glucagon-like peptide-1 receptor agonist (GLP-1 RA)
- Insulin
- Acarbose
- TZD

If HbA1c target not achieved in three months:

- check and review current therapies, stop any that fail to improve glycaemic control
- check patient understanding and self-management
- review use of therapies
- exclude other comorbidities/therapies impacting on glycaemic control
Third line: Consider triple oral therapy or addition of GLP-1 RA or insulin

- SU
- DPP-4i
- SGLT2i
- GLP-1RA
- Insulin*
- Acarbose
- TZD

If HbA1c target not achieved in three months:
- check and review current therapies, stop any that fail to improve glycaemic control
- check patient understanding and self-management
- review use of therapies
- exclude other comorbidities/therapies impacting on glycaemic control

THEN

If on triple oral therapy
- Switch ≥1 oral agent to GLP-1 RA or insulin* or another oral agent*

If on GLP-1 RA
- Change to basal or premixed insulin*
- Add basal or premixed insulin*

If on basal insulin*
- Add SGLT2 inhibitor or GLP-1 RA or basal bolus or basal plus insulin

Australian blood glucose treatment algorithm for type 2 diabetes

Determine the individual's HbA1c target – this will commonly be <53 mmol/mol (7%). If not at target, or if an HbA1c reduction of >0.5% is not achieved after three months, move down the algorithm.

Reproduced with permission from the Australian Diabetes Society.
ADULT WITH TYPE 2 DIABETES WHO CAN TAKE METFORMIN

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:
- Offer standard-release metformin
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%)  

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider dual therapy with:
  - metformin and a DPP-4i
  - metformin and pioglitazone
  - metformin and an SU
  - metformin and an SGLT-2
d- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider:
  - triple therapy with:
    - metformin, a DPP-4i and an SU
    - metformin, pioglitazone and an SU
    - metformin, pioglitazone or an SU, and an SGLT-2
  - insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

METFORMIN CONTRAINDICATED OR NOT TOLERATED

If standard-release metformin is not tolerated, consider a trial of modified-release metformin

If triple therapy is not effective, not tolerated or contraindicated, consider combination therapy with metformin, an SU and a GLP-1 mimer for adults with type 2 diabetes who:
- have a BMI of 35 kg/m² or higher (adjust accordingly for people from black, Asian and other minority ethnic groups)
- have a BMI lower than 35 kg/m², and for whom insulin therapy would have significant occupational implications, or weight loss would benefit other significant obesity-related comorbidities

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider dual therapy with:
  - a DPP-4i and pioglitazone
  - a DPP-4i and an SU
  - pioglitazone and an SU
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

Nice May 2017
ADA 2018 Standards of Care

At diagnosis, initiate lifestyle management, set AIC target, and initiate pharmacologic therapy based on AIC:

- AIC is less than 8%, consider Monotherapy.
- AIC is greater than or equal to 9%, consider Dual Therapy.
- AIC is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, consider Combination Injectable Therapy (See Figure 8.2).

**Monotherapy**

Lifestyle Management + Metformin

Initiate metformin therapy if no contraindications (See Table 8.1)

**Lifestyle Management + Metformin + Additional Agent**

ASCVD? Yes:
- Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with "a" on p. 575 and Table 8.1)

Yes:
- Add second agent after consideration of drug-specific effects and patient factors (See Table 8.3)

**Lifestyle Management + Metformin + Two Additional Agents**

Add third agent based on drug-specific effects and patient factors (See Table 8.1)

**Combination Injectable Therapy** (See Figure 8.2)
- Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

Add third agent based on drug-specific effects and patient factors* (See Table 8.1)
Individualising HbA$_{1c}$ goals

Inzucchi et al. Diabetes Care 2012;35:1364–79
Newer agents

- Incretin Pathway
- SGLT2 inhibitors
Incretin Pathways: GLP-1 Actions in Peripheral Tissue

### Side Effects: GLP-1 Receptor Agonists and DPP-4 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>GLP-1 Receptor Agonists</th>
<th>DPP-4 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Side effects</strong></td>
<td>Gastrointestinal</td>
<td>Well tolerated</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>&gt; 85% patients lose weight</td>
<td>Weight neutral</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Twice-daily injection</td>
<td>Oral, once daily</td>
</tr>
<tr>
<td><strong>Other cardiac risk factors</strong></td>
<td>↓ Triglycerides ↑ HDL ↓ Blood pressure</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

DPP4 inhibitors

- **Januvia** (Sitagliptin) (NZ Approved)
- **Galvus** (Vildagliptin) (NZ Approved)
- **Onglyza** (Saxagliptin) (NZ Approved)
- **Tradjenta** (Linagliptin)
GLP 1 agonists

- **exenatide** (Byetta/Bydureon), approved in 2005/2012 *(NZ Approved)*
- **liraglutide** (Victoza, Saxenda), approved 2010
- **lixisenatide** (Lyxumia), approved in 2016 *(NZ not available)*
- **albiglutide** (Tanzeum), approved in 2014
- **dulaglutide** (Trulicity), approved in 2014
- **semaglutide** (Ozempic), approved in 2017.
LEADER trial: Primary Outcome

First occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke in the time-to-event analysis in patients with type 2 diabetes and high CV risk.

Hazard ratio, 0.87 (95% CI, 0.78–0.97)  
P<0.001 for noninferiority  
P=0.01 for superiority  

Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial
LEADER trial:
Death from Cardiovascular Causes

Hazard ratio, 0.78 (95% CI, 0.66–0.93)  
P=0.007

Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial
SGLT-2 inhibitors

- canagliflozin (Invokana) first for FDA approval (2013)
- dapagliflozin (Forxiga/Farxiga) (NZ approved)
- empagliflozin (Jardiance)
Renal glucose reabsorption in patients with hyperglycaemia

Filtered glucose load >180 g/day

SGLT 1

SGLT 2

SGLT, sodium glucose cotransporter. Gerich JE. *Diabet Med* 2010;27:136
Empagliflozin increases urinary glucose excretion via SGLT2 inhibition

Filtered glucose load >180 g/day

SGLT2 inhibitors reduce glucose reabsorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis

*SGLT, sodium glucose cotransporter.

*Loss of ~ 80 g of glucose per day = 240 cal/day.

Bakris GL et al. Kidney Int
Renal anatomy and physiology

Afferent arteriole
Vasoconstriction decreases GFR

Efferent arteriole
Vasoconstriction increases GFR

Key
Flow of blood
Flow of filtrate

Bowman’s capsule
Proximal convoluted tubule

GFR, glomerular filtration rate
Cherney D et al. Circulation
2014:129:587

76
Empagliflozin exerts a hemodynamic effect within the kidney

• By restoring the Tubulo-Glomerular Feedback (TGF), empagliflozin increases the afferent arteriole tone, thereby lowering glomerular hypertension

Action:
- Afferent arteriole narrowing

Clinical implications:
- Glomerular pressure decreases
- Early clinical marker:
  - Initial dip in GFR
  - Reduction of albuminuria

SGLT, sodium glucose cotransporter; GFR, glomerular filtration rate. Adapted from: Cherney D et al. Circulation 2014;129:587, Skrtic M et al. Diabetologia 77. SGLT2 inhibition Afferent arteriole narrowing
CV death

JARDIANCE® reduced the relative risk of CV death by 38%
vs placebo on top of standard of care in patients with T2D and established CV disease (CAD, PAD, MI or stroke)\(^1\)

\[HR = 0.62, \quad p < 0.001\]

Early* and sustained# response

Results achieved on top of standard of care
• Antihypertensives
• Lipid lowering agents
• Anticoagulants
• Glucose lowering agents

*Within 6 months from start. #Up to 48 months from start.
CV death was a pre-specified secondary endpoint. Cumulative incidence function. HR, hazard ratio
The absolute risk for CV death was 5.9% in patients receiving standard of care plus placebo and was reduced to 3.7% in patients receiving standard of care plus JARDIANCE® (p < 0.001).\(^1\)

All-cause mortality

JARDIANCE® reduced the relative risk of all-cause mortality by 32% vs placebo on top of standard of care in patients with T2D and established CV disease (CAD, PAD, MI or stroke)\(^1\)

JARDIANCE® is not indicated to reduce all-cause mortality

---

HR 0.68  
\(p<0.001\)

---

All-cause mortality was a pre-specified secondary endpoint. Kaplan-Meier estimate. HR, hazard ratio

The absolute risk for all-cause mortality was 8.3% in patients receiving standard of care plus placebo and was reduced to 5.7% in patients receiving standard of care plus JARDIANCE® (p<0.001).\(^1\)

Hospitalisation for heart failure

JARDIANCE® reduced the relative risk of hospitalisation for heart failure by **35%**
vs placebo on top of standard of care in patients with T2D and established CV disease (CAD, PAD, MI or stroke)\(^1\)

JARDIANCE® is not indicated to reduce hospitalisation for heart failure

*Early*\(^*\) and sustained*\(^*\) response

![Graph showing hospitalisation rates over time with JARDIANCE and placebo](image)

**HR 0.65**  
*p=0.002*

*Within 6 months from start. \(^*\)Up to 48 months from start.*

Hospitalisation for heart failure was a pre-specified secondary endpoint. Cumulative incidence function. HR, hazard ratio

The absolute risk for hospitalisation for heart failure was 4.1% in patients receiving standard of care plus placebo and was reduced to 2.7% in patients receiving standard of care plus JARDIANCE\(^\circledast\) (p<0.002)\(^1\)


**Results achieved on top of standard of care**
- Antihypertensives
- Lipid lowering agents
- Anticoagulants
- Glucose lowering agents
For comparison:

RENAAL Patients Reaching the Primary Composite Endpoint*

Risk reduction = 16%
P = 0.02

Cumulative % of patients with event

For comparison:

©2001 Massachusetts Medical Society. All rights reserved.
Figure 3. Median Changes from Base Line in the Level of Proteinuria. Proteinuria was measured as the urinary albumin-to-creatinine ratio in a first morning specimen. The mean follow-up time was 3.4 years.
RENAAL First Hospitalization for Heart Failure

% of patients with event

32% Risk reduction
P=0.005

Placebo* (n) 762 685 616 375 53
Losartan* (n) 751 701 637 388 74

Cardiovascular Risk

- Treatment is based on either:
  - Clinical high risk (secondary prevention)
  - Calculated risk (www.nzssd.org.nz/cvd/)
Prolactin

- Normal physiology
- Disease and Prolactin
- Antipschotics
- Does hyperprolactinaemia matter? How?
- Approaches to manage or minimise hyperprolactinaemia
Prolactin

- Anterior pituitary hormone
- Discovered in early 1970s
- Inhibited by dopamine released from hypothalamus via D₂ receptors
- Other neurotransmitters/hormones may have stimulatory effect on PrL release including VIP and serotonin
- Normal range 40–600 mIU/l
Prolactin physiology

- Episodic secretion with sleep-dependent diurnal variation
- Increase 10 fold during pregnancy principally in response to oestrogen
- 4–6/52 postpartum remains elevated, with suckling triggering episodic release
- 6–12/52 postpartum basal levels fall to normal, but suckling produces high peaks
- other physiologic stimuli for release include exercise, sexual activity, acute psychological stress
Prolactin in pregnancy
Prolactin levels postpartum
Disease and Prolactin

- Pituitary Disease
- Drugs
- Stress
- Nipple stimulation/chest wall trauma
- Hypothyroidism
- Oestrogen (high dose)
- Renal disease/clearance of prolactin
Consequences of elevation of PrL:

- Hypogonadism
- Galactorrhoea
- (mild androgenic effects)
Hyperprolactinaemia by Aetiology

- Lactotroph macroadenoma
- Lactotroph microadenoma
- Other pituitary and hypothalamic disease
- Pregnancy
- Stress
- Drugs
(Partial) list of drugs known to cause hyperprolactinemia and/or galactorrhea

- **Typical antipsychotics** Phenothiazine drugs (*eg*, chlorpromazine, clomipramine, fluphenazine, prochlorperazine, thioridazine) haloperidol, pimozide
- **Atypical antipsychotics** risperidone, molindone olanzapine
- **Antidepressant agents** clomipramine, desipramine
- **Gastrointestinal drugs** cimetidine, metoclopramide
- **Antihypertensive agents** methyldopa, reserpine, verapamil
- **Opiates** codeine, morphine
Currently no published data.

Frequency: ++ = high frequency; + = moderate frequency; ++ = marked elevation; ↓↓ = minimal frequency; ↓↓ = no or minimal elevation; ↓↓ = mild elevation; ↓↓ = moderate elevation of PRL level is dose-related (see text).

a. Lower therapeutic doses may have minimal effects since incidence estimated from the literature.

b. After some weeks of therapy. Following single oral dose of first week of therapy.

c. These incidence rates may not be directly comparable.

d. In some patients, PRL elevation occurs with some oral contraceptives.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hypoprolactinemia</th>
<th>Sustained</th>
<th>Early</th>
<th>PR elevation</th>
</tr>
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<tbody>
<tr>
<td>Ziperdione</td>
<td>↓↓↓↓↓</td>
<td>↓↓↓↓↓</td>
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</tr>
</tbody>
</table>

Table IV. Representative traditional and atypical antipsychotics and their estimated effects on prolactin (PRL) level at therapeutic doses.
Acute dose comparison

**FIGURE 1.** Mean Plasma Prolactin Level Changes Over 24 Hours in 18 Patients After Taking Clozapine, Olanzapine, or Risperidone and in Five of the Same Patients After Not Taking the Drugs

- Clozapine (N=6)
- Olanzapine (N=6)
- Risperidone (N=6)
- Combined drug-free patients (N=5)

Note: One of the patients taking clozapine, two taking olanzapine, and two taking risperidone had their prolactin levels measured twice: first after taking their usual dose of the medication and second, at least 1 month later, after not taking their usual dose.

Am J Psychiatry 2002; 159:133–135
## Novel Antipsychotics

<table>
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<tr>
<th>Agent</th>
<th>D&lt;sub&gt;2&lt;/sub&gt; Blockade</th>
<th>5 HT&lt;sub&gt;2&lt;/sub&gt; Blockade</th>
<th>Other Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>weak</td>
<td>potent</td>
<td>Anti muscarinic histamine blockade</td>
</tr>
<tr>
<td>Risperidone</td>
<td>potent</td>
<td>potent</td>
<td>Anti muscarinic</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>weak</td>
<td>potent</td>
<td>Alpha blockade, histamine blockade</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>weak</td>
<td>moderate</td>
<td></td>
</tr>
</tbody>
</table>
Hyperprolactinaemia in patients on antipsychotics

• *May be physiological*
• *May be due to other illness*  
  (hypothyroidism, pituitary disease)
• *May not be associated with symptoms*
• *Symptoms may not be problematic*  
  (eg hypogonadism in a women on COC or DP)
With respect to pituitary disease:

- Elevated prolactin does not always require treatment:
- Few/no sx (esp postmenopausal woman)
- Small tumor not invasive or compressing structures
With respect to pituitary disease:

- Normal prolactin does not exclude pituitary disease
- Elevated prolactin does not usually interfere with gonadal function if PrL < 1000
- Elevated prolactin due to dopamine blockade is not known to cause pituitary tumor development or growth

- However, markedly elevated prolactin levels in a pt with a pituitary tumor may be an indication for urgent medical treatment
Indications for medical management of Prolactinomas

Mass Effects
• Hypopituitarism
• Visual field defects due to pressure on the optic chiasm
• Cranial nerve deficits
• Headaches

Effects of Hyperprolactinemia
• Hypogonadism
• Amenorrhea or oligoamenorrhea
• Infertility
• Impotence
• Osteoporosis or osteopenia

Relative indications:
• Bothersome hirsuitism
• Bothersome galactorrhea

Gillam et al, Endocrine Reviews 2006
Management of Antipsychotic-induced hyperprolactinaemia

• Exclude other causes
  – (Pre-treatment level, TFT’s)

• Treat if problematic symptoms/s-e
  – ?Oestrogen/progesterone
  – ?substitution
  – ?combination Tx
  – ?addition of dopaminergic agents
"It's no good, Dawson! We're being sucked in by the sun's gravitational field and there's nothing we can do! ... And let me add those are my sunglasses you're wearing!"
Thyroid function

- Thyroid normally under tonic stimulus and negative feedback (ie TSH dependent)
- Hypothyroidism associated with weight gain and hyperprolactinaemia
- Lithium has complex effects on thyroid function
Lithium and Thyroid

noted that patients with psychiatric disease treated with lithium carbonate developed hypothyroidism and goiter.

Lithium:

• increases intrathyroidal iodine content,
• inhibits the coupling of iodotyrosine residues to form iodothyronines (thyroxine [T4] and triiodothyronine [T3]), and
• inhibits release of T4 and T3
Lithium and Thyroid

- Goitre 40-50% usually in first 2 years
- 20-30% may develop hypothyroidism
  - May be associated with thyroid autoimmunity
  - More rarely with hyperthyroidism or thyroiditis (transient thyrotoxicosis)
Summary

• Endocrine conditions are common in patients with psychiatric illness
  – Should be screened for
• These conditions may affect patient care and long term morbidity and mortality
  – Require attention (monitoring and management)
• Psychiatric treatment may predispose to endocrine problems (and other physical disease aspects)
  – Duty of care
Thanks for your attention!!!