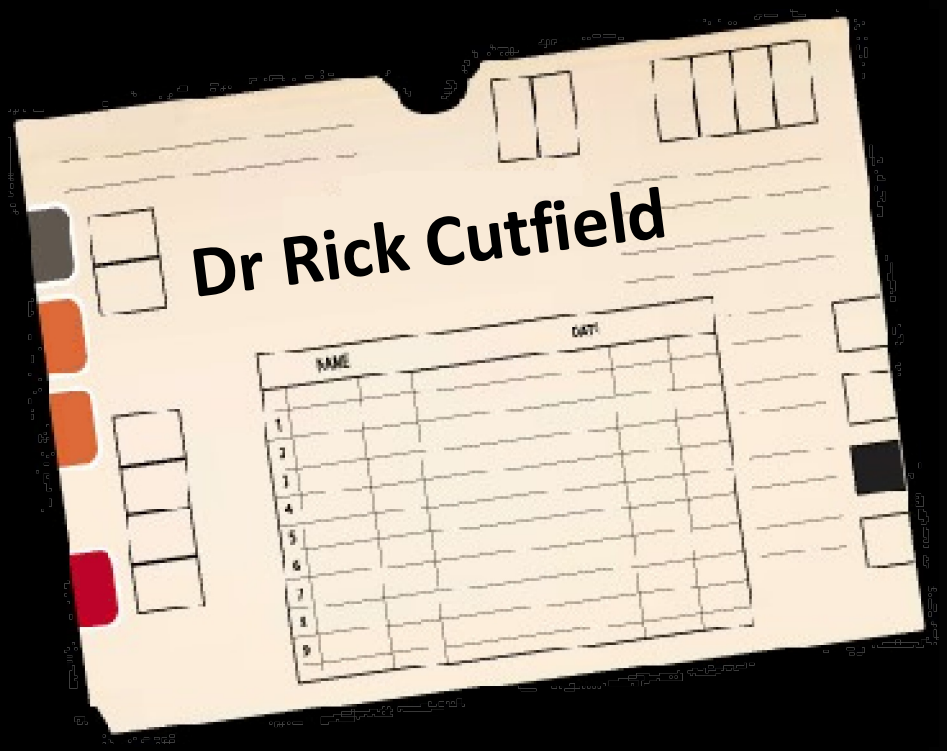
Insulin use in Type 2 Diabetes



Conflict of Interest

- I have been on advisory boards or had speaker fees from the following pharmaceutical companies:
  - Eli Lilly
  - Novo Nordisk
  - Sanofi Aventis
  - MSD
  - Astra Zeneca
- I have been on the New Zealand Guideline Group for Diabetes and past member of PTAC Diabetes subcommittee for Pharmac.

Other Conflicts of Interest

- Work vs leisure balance
- When to retire?
- Continue to support the Blues Rugby Team or move to Hamilton

The Diabetes Burden

- Prevalence and incidence of T2 Diabetes increasing in conjunction with:
  - ↑ obesity rates
  - westernisation of lifestyles
  - Ageing
  - Ethnicity
- Up to 12% of health budget.

- Leading cause of:
  - Cardiovascular disease
  - Blindness
  - End stage renal failure
  - Amputations
  - Hospitalisations
- Associated with ↑ risk of:
  - Cancer
  - Psychiatric illness
  - Cognitive decline
  - Chronic liver disease
  - Accelerated arthritis

SORTING OUT A TARGET

What does the evidence say?

Relationship of Glycaemia Control to Outcome

UKPDS:

- Newly diagnosed Type 2
- For every 1% decrease in HbA1c there was a
  - 37% risk reduction in microvascular complaints
  - 21% risk reduction in diabetes-related death
  - 14% risk reduction in myocardial infarct
- Metformin had 40-50% ↓ in mortality, and M.I. despite only 0.6% difference in HbA1c

Relationship of Glycaemia Control to Outcome

10 YEARS AFTER UKPDS:

- Despite now similar HbA1c between two groups
- Benefits maintained including CVD rates and mortality, i.e. EARLY maintenance of glycaemic control matters.

Relationship of Glycaemia Control to Outcome

2008 – ACCORD / ADVANCE / VADT studies:

- Compared two levels of glycaemic control on C.V. end points in middle-aged/older patients with well established T2DM at high C.V. risk.
- Aim HbA1c < 6% or <6.5%.
- No benefit in driving HbA1c to less than 6.5% (42mmol/mol) and Accord showed 22% ↑ mortality in so doing.
- Probable 15% risk reduction in non-fatal M.I. for 1% decrease in HbA1c but no benefits in all cause mortality for this group.

Relationship of Glycaemia Control to Outcome

Conclusion:

- Very tight control in people with very high C.V. risk with long standing T2 diabetes not justified unless easily done with diet/metformin.
- HbA1c target needs to be individualised from 50-55 up to 65 mmol/mol.

Glycaemic Targets

- Individualise, e.g.

1. HbA1c ≤ 50 – 53 mmol/mol
   - Short disease duration
   - Long life expectation
   - No significant C.V.D.
   - Achievable without significant hypoglycaemia with simple regimens

2. HbA1c ≥ 55-65 mmol/mol
   - Limited life expectancy
   - Advanced complications
   - Extensive co-morbidities
   - Lower targets extremely difficult despite best efforts
   - History of severe hypoglycaemia

Glycaemic Targets

- **SMBG**
  - Fasting < 7mmol/L
  - Postprandial <10mmol/L ideal

Patient-Centred Approach

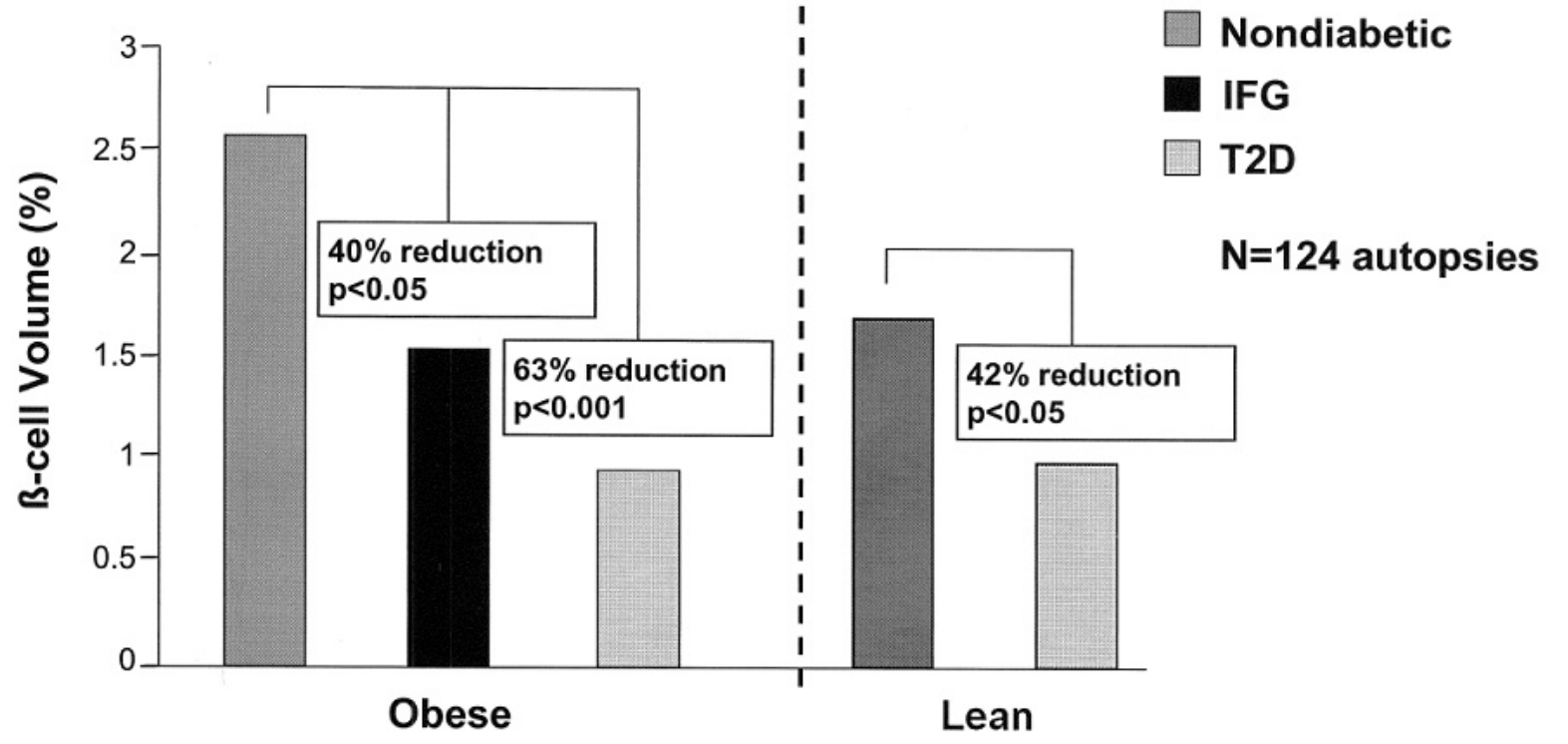
"Providing care that is respectful of and responsive to individual patient preferences, needs and values and ensuring that patient values guide all clinical decisions.'

Engaging patients in health care decisions may enhance adherence to therapy.

In T2 Diabetes

- Insulin resistance
- Abnormal islet cell function – progressive loss of ß cells (glucolipotoxicity) and ß cells function.
- Abnormalities in incretin system especially GLP-I which influences insulin and glucagon secretion, gastric emptying and appetite.
- All may be reversible with weight loss.

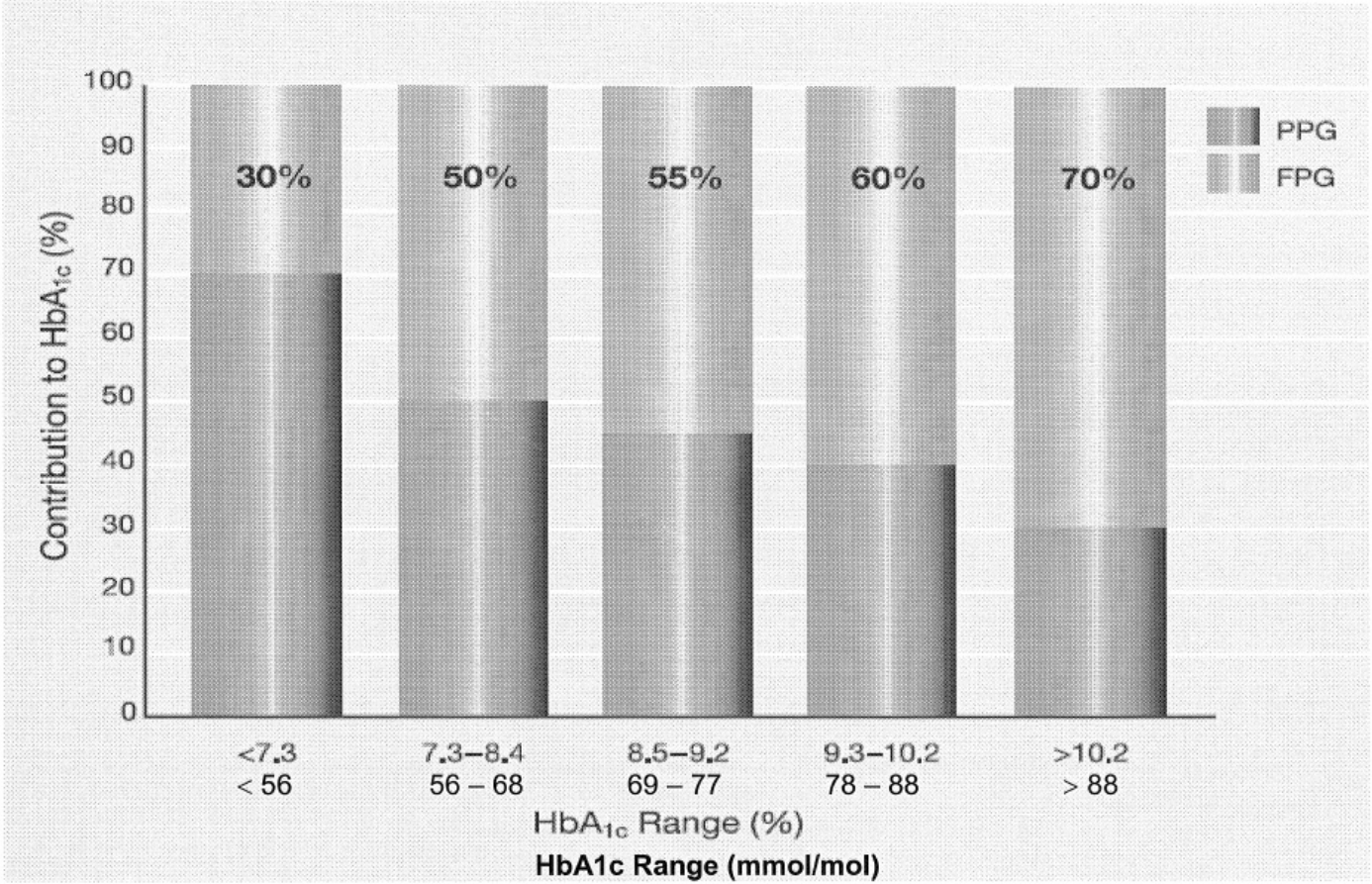
ß-Cell Volume Reduced 40% in Patients with IFG and up to 60% in Patients with T2D



ß=beta; IFG=impaired fasting glucose; T2D=type 2 diabetes.

Derived from Butler et al. *Diabetes* 2003; 52(1):102-10.

Contribution of FBG and PPBG to Overall Diurnal Hyperglycaemia



Monnier L et al, *Diabetes Care* 26:3,881-885, 2003

Principles of Management Prior to Medication

Lifestyle:

- Personalised diet advice vs groups
- 5-10% weight loss is helpful. Realism.
- Exercise – ideal 150 min / week but any increase is good
- Use for 3 months before medication if likely to be successful
- Weight loss hard to sustain

Oral Agents

Metformin is drug of choice

- 10% G.I. side effects – take with/after food
- Titrate to 2.5gms / day – use B.D. to aid compliance
- Can use if egfR >30ml/min
- Benefits in terms of ↓ C.V. Disease ?? Cancer

Other Oral Drugs

1. Sulphonylureas
   - Cheap
   - B.D.
   - Risk of hypoglycaemia esp in elderly
   - May increase rate of ß cell failure

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   - Once daily
   - Helps fatty liver
   - But weight gain; oedema; ↓ bones density and ↑ fractures; heart failure <u>if at risk</u>

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or 3. DPP4 – Inhibitors (e.g. Sitagliptin)
   - No hypoglycaemia if used with Metformin
   - Weight neutral
   - Funding likely this year

Consider

- Acarbose
  - Mild
  - G.I. side effects

- Injectable GLP agonist
  (e.g. Exanatide / Liraglutide)
  - Weight loss with glucose lowering
  - Instead of insulin ?
  - Once weekly injection imminent
  - Potentially big future

Consider BARIATRIC SURGERY if BMI > 35 and duration of diabetes less than 10 years

Even consider intermittent modified VL Calorie Diet, e.g. Optifast for 8-10 weeks.

May improve ß cell function and medication dependency

Taylor et al Lancet 2012

And or Crucial Importance

- Always attack other C.V. risk factors
- Assess risk and where appropriate:
  - Statin to ↓ LDL to < 1.7 – 2.0
  - ACE-I esp if microalbuminura or BP >135-140mmHg systolic
  - Aspirin if C.V. risk ≥ 15%

[NZSSD C.V. Risk Assessment - http://www.nzssd.org.nz/cvd/]

Insulin

Start if:

a) Lifestyle / oral agents maximised

b) HbA1c ≥ 60-65 on average in younger
≥ 65-70 in older
especially if symptomatic and if safe

c) Consider earlier if GAD Ab +ve
(ß cell function decreases faster)
Perhaps earlier insulin protects remaining ß cells ??

d) Severely symptomatic with HbA1c > 100mmol/mol even after diagnosis

Is insulin delayed too long?

Clinical Inertia in T2DM Management in Auckland

Study of 2240 patients in 1° care in S.W. Auckland in 2004-2006 on 2 oral agents:

- 954 (42.6%) of these had HbA1c ≥ 8%

Nearly 2 year Later:

- 451 out of 605 patients with second HbA1c ≥ 8 were still not on insulin

Choe & Cutfield 2008

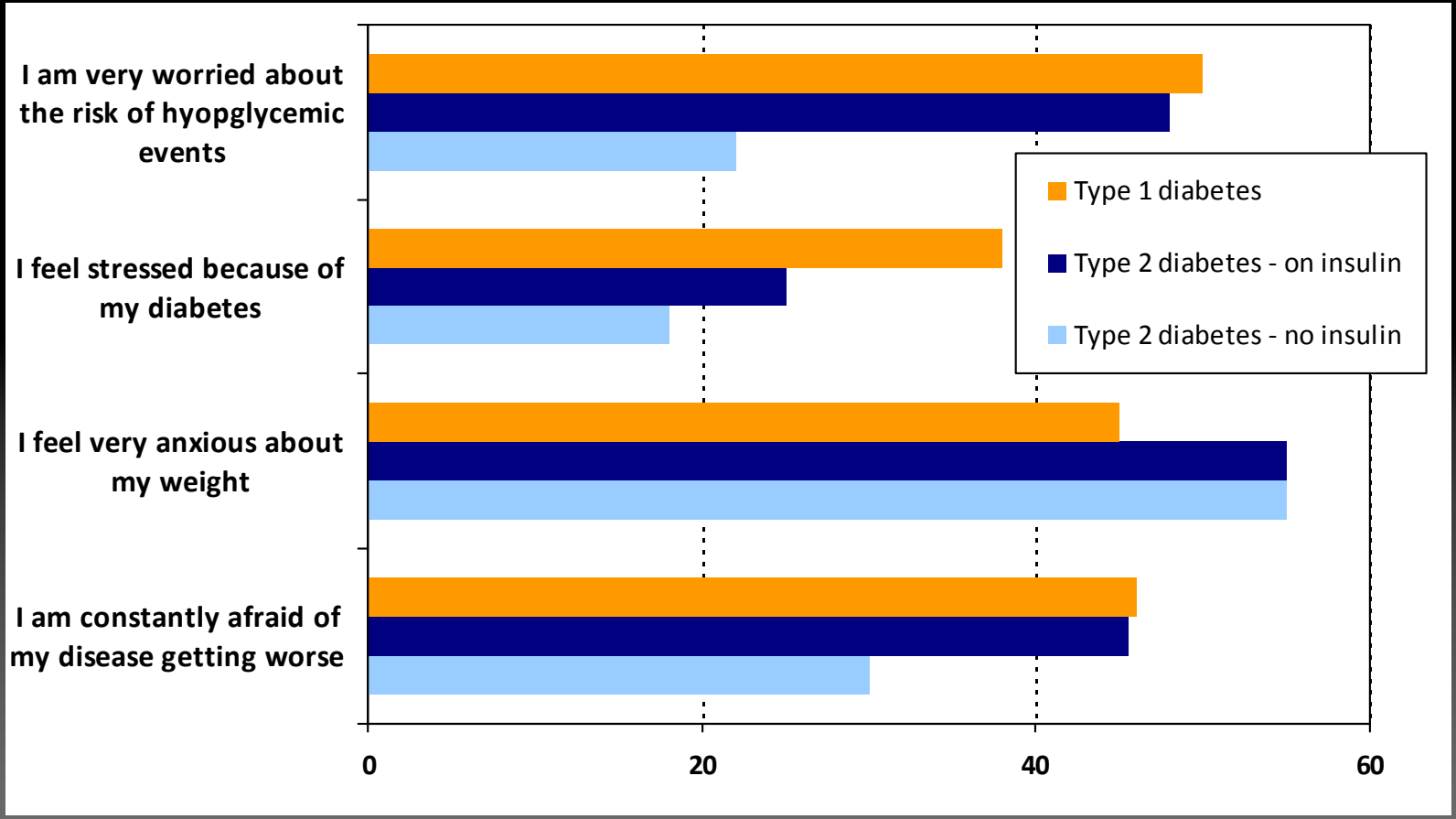
Targets reached more easily if not delayed

DAWN Study – Australian Results

Anxieties about Diabetes

(% of participants fully agree or mainly agree)

Question: Please rate, on a 4-point scale, to what extent you agree with the following statements related to diabetes (fully disagree, mainly disagree, mainly agree, fully agree).

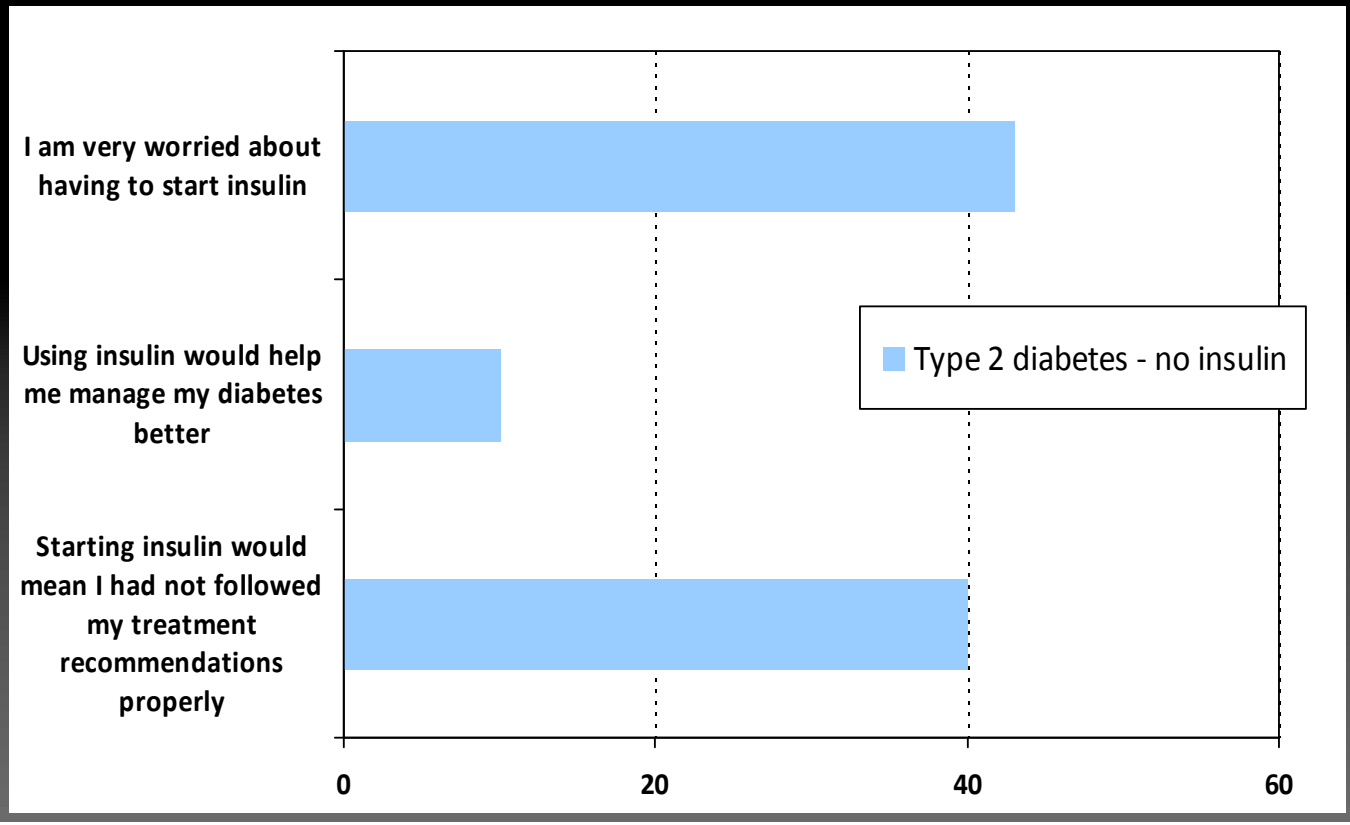


DAWN Study – Australian Results

Concerns about commencing insulin in people with Type 2 diabetes not treated with insulin

(% fully agree or mainly agree)

Questions: {Please rate, on a 4-point scale, to what extent you agree with the following statements related to diabetes (fully disagree, mainly disagree, mainly agree, fully agree)?



Barriers to Insulin

Patient:

- Fear of injections
- Perception of failure
- Social issues / employment
- Fear of complications (misinformation largely)
- Fear of hypos; weight gain
- Other priorities, esp if feeling “well”

Barriers to Insulin

Doctor:

- Complexity of insulin regimens
  Experience / education / confidence
- **Time / Resources / Costs**
- Practice Nurse training / time
- Concerns re hypos / weight and poor compliance

Overcoming Barriers to Improved Diabetes Care and Insulin Use

- GP / Practice Nurse education with continued support from DN Specialist and/or Endocrinologist
- Practice Nurse / GP champions
- Regular update – personal contact preferable
- Use diabetes clinics (know at least your local specialist nurse or endo) esp. community-based if needed.
- Funding:
  - Nurse clinics ?
  - High needs patients
- Review diabetes patients in your practice – see how they are doing – discuss in forums together.

Overcoming Barriers to Insulin

Marketing:

- Introduce concept of insulin deficiency early
- Modern insulin unlikely to cause significant hypo
- Weight gain minimised by continuing MET and lifestyle measures
- Use simple regimens to start with
- Use 4mm pen needles – virtually painless – plus latest pen devices
- Sell the benefits of improved glycaemic control including "feeling better" in many
- Importantly, tell the patient they are not "failures" for needing insulin
- Opportunistic injecting during consult

There are Many Ways to Start Insulin

- Difference between insulins are not large

SO

- Be familiar with 1 or 2 insulins and keep it SIMPLE and SAFE

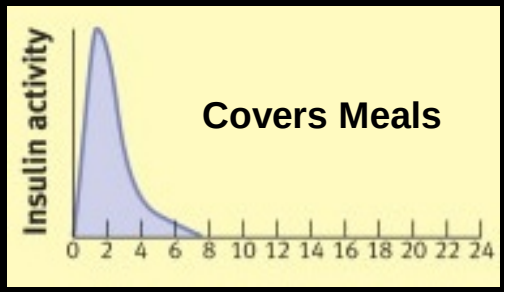
Insulins Available

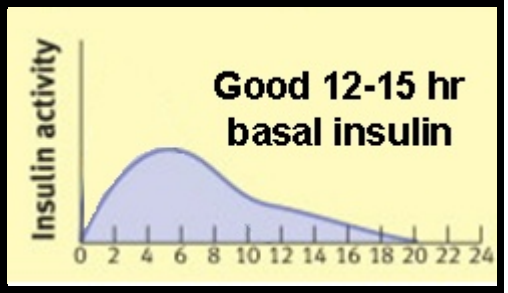
1. **"Rapid Acting"**
   e.g. Humalog, Novorapid, Apidra

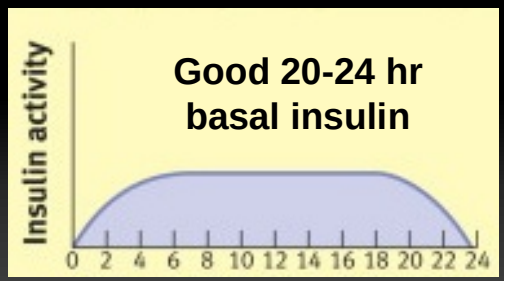
2. **"Intermediate Acting"** NPH Insulin
   e.g. Humulin N or Protophane

3. **"Long Acting"** Basal
   e.g. Glargine (Lantus)

4. **Premixed Insulins**
   25% Rapid 75% NPH — Humalog Mix 25
   [30% Rapid 70% NPH — Novomix 30 (soon to be available)]
   30% Regular 70% NPH — Mixtard / Penmix 30/70





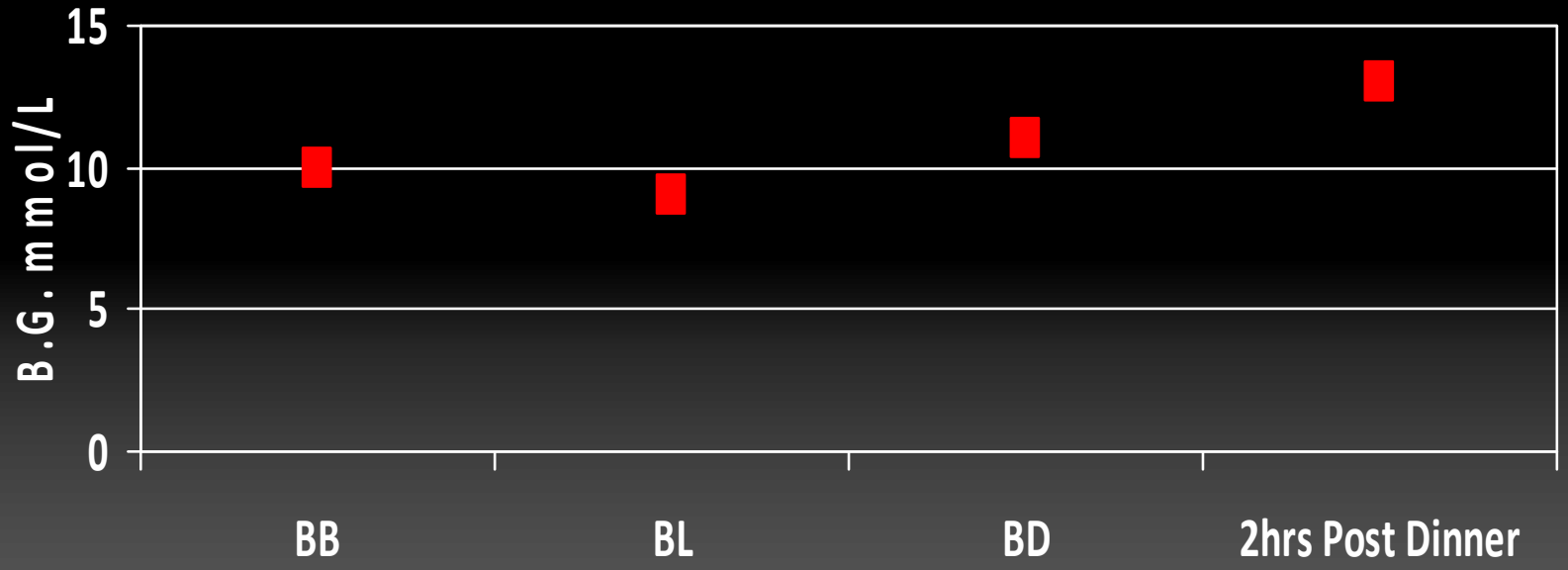


Principles of starting insulin in Type 2 DM

- Education
- Review patients preferred food programme
- Look at glucose profiles to decide insulin type
- Continue METFORMIN and probably at first, sulphonylurea if using basal insulin
- Basal insulin to start with at lowish doses initially
- Patient learns to titrate insulin according to pre-defined B.G. target.

B.G. Profile - Patient 1:

- On MET 850mg 1700mg : Gliclazide 160mg B.D.
- HbA1c 70mmol/mol



- High fasting glucose
  (↑ hepatic glucose production overnight)

B.G. Profile - Patient 1:

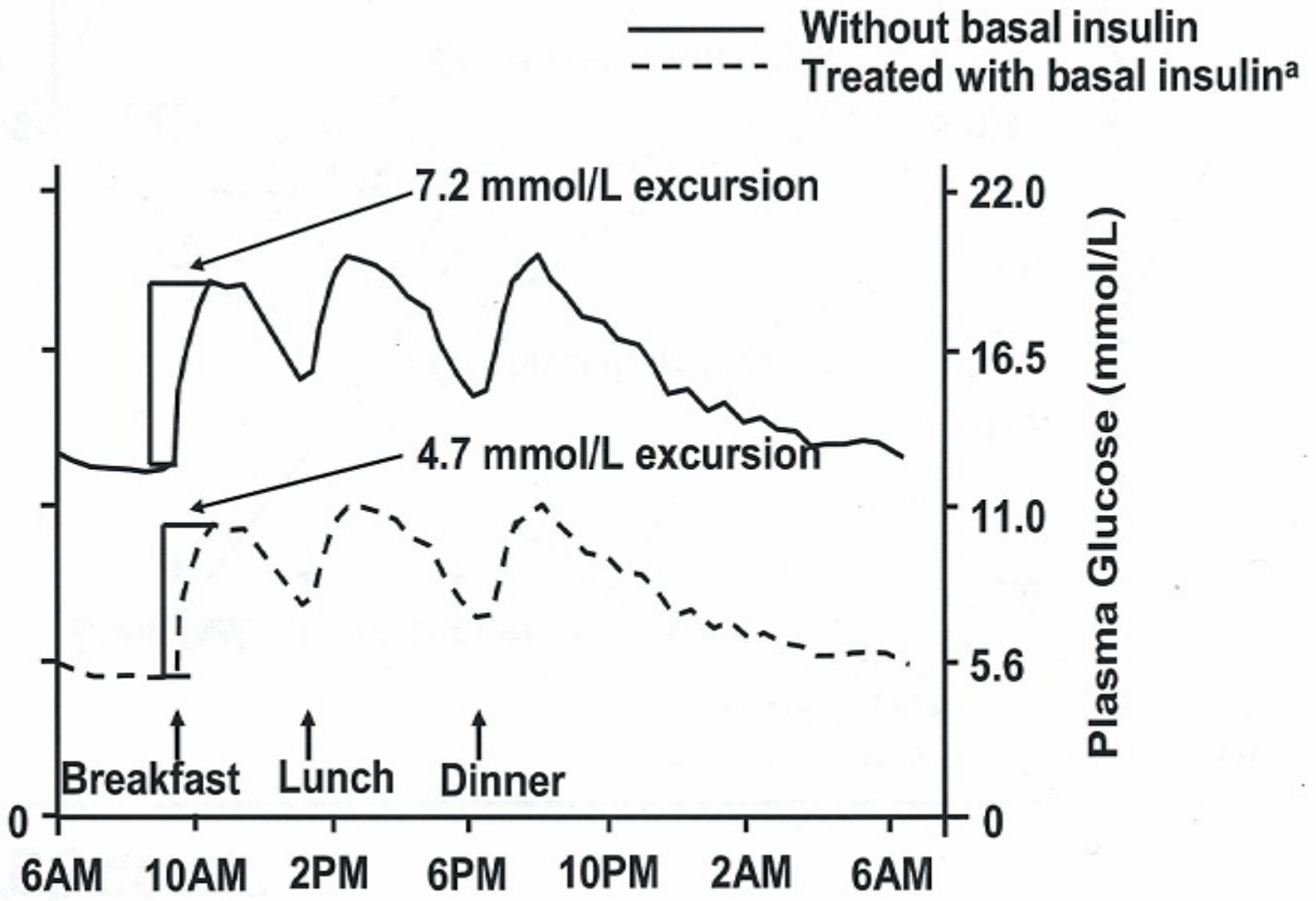
- Start insulin with bedtime basal

  a) NPH e.g. Humulin N / Protophane
     [See N.Z. Guidelines 2011]

  or possibly

  b) Lantus (glargine)

Basal Insulin can reduce Hyperglycaemia in T2D



T2D=type 2 diabetes.

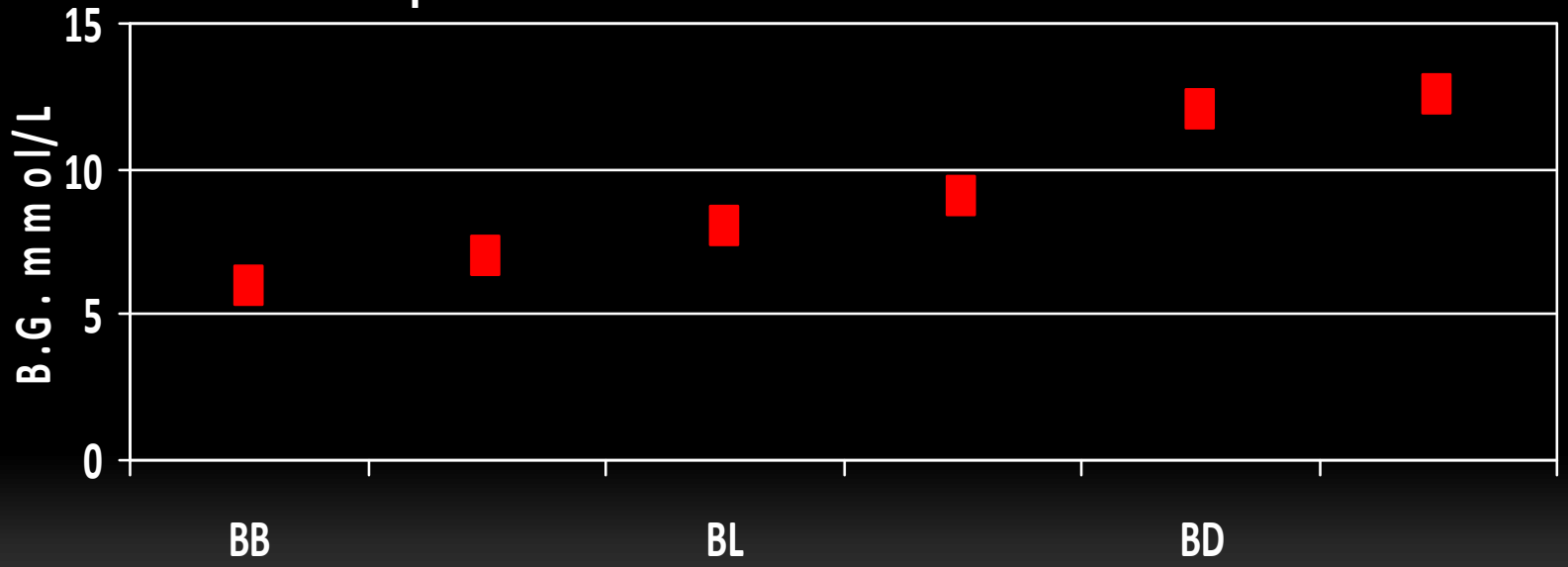
[a]Basal insulin is neutral protamine hagedorn insulin or insulin glargine.

B.G. Profile - Patient 1:

- Continue MET / Reduce gliclazide to 80mg B.D.
- Use 8-10u insulin to start
- Pt can titrate by 2-3 units every 4-5 days till fasting glucose at 5-7mmol/L
- Frequent contact with practice nurse / G.P. initially

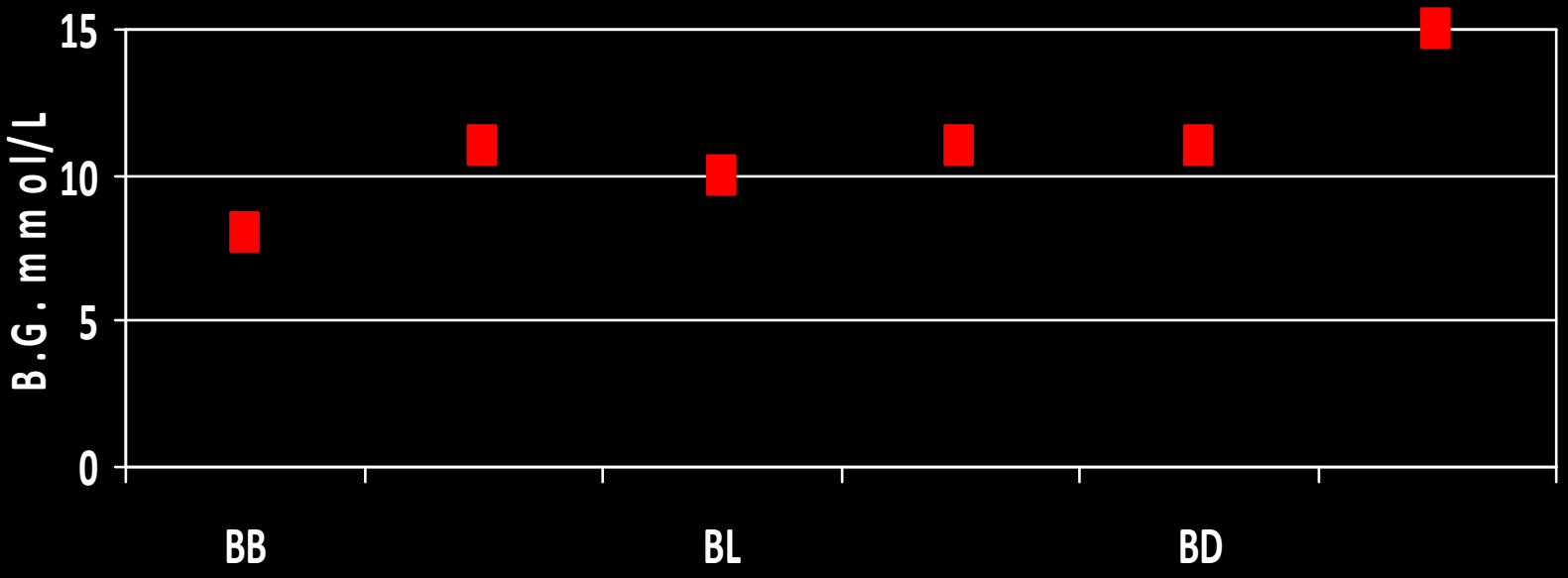
B.G. Profile:

- If HbA1c not at target review B.G. profile including pre and 2 hrs post meal



- Here B.G. is drifting up in day despite noctural NPH
- Could: a) add B.D. NPH insulin,
  e.g. 8u am 10-12u evening
  or b) Lantus insulin once daily,
  e.g. 16-18u nocte

Patient 2:



- In this situation high levels (over 10) occur after breakfast and dinner especially.
- Consider short-acting insulin at dinner and breakfast as pre-mix, e.g. Humalog Mix 25 (25% Humalog 75% Hum N) at breakfast and dinner at 8-10u BB 10-12U BD.

Pre-Mixed Insulins

e.g. Humalog Mix 25; Penmix 30

- Usually improves HbA1c after basal insulin alone, if moderate carbohydrate intake is eaten regularly
- Convenience with 1 injection at meal once or twice (usually) daily
- Post meal coverage but not flexible if carbohydrate intake at meals varies significantly

Other Insulin Regimens

"Lantus Plus 1"

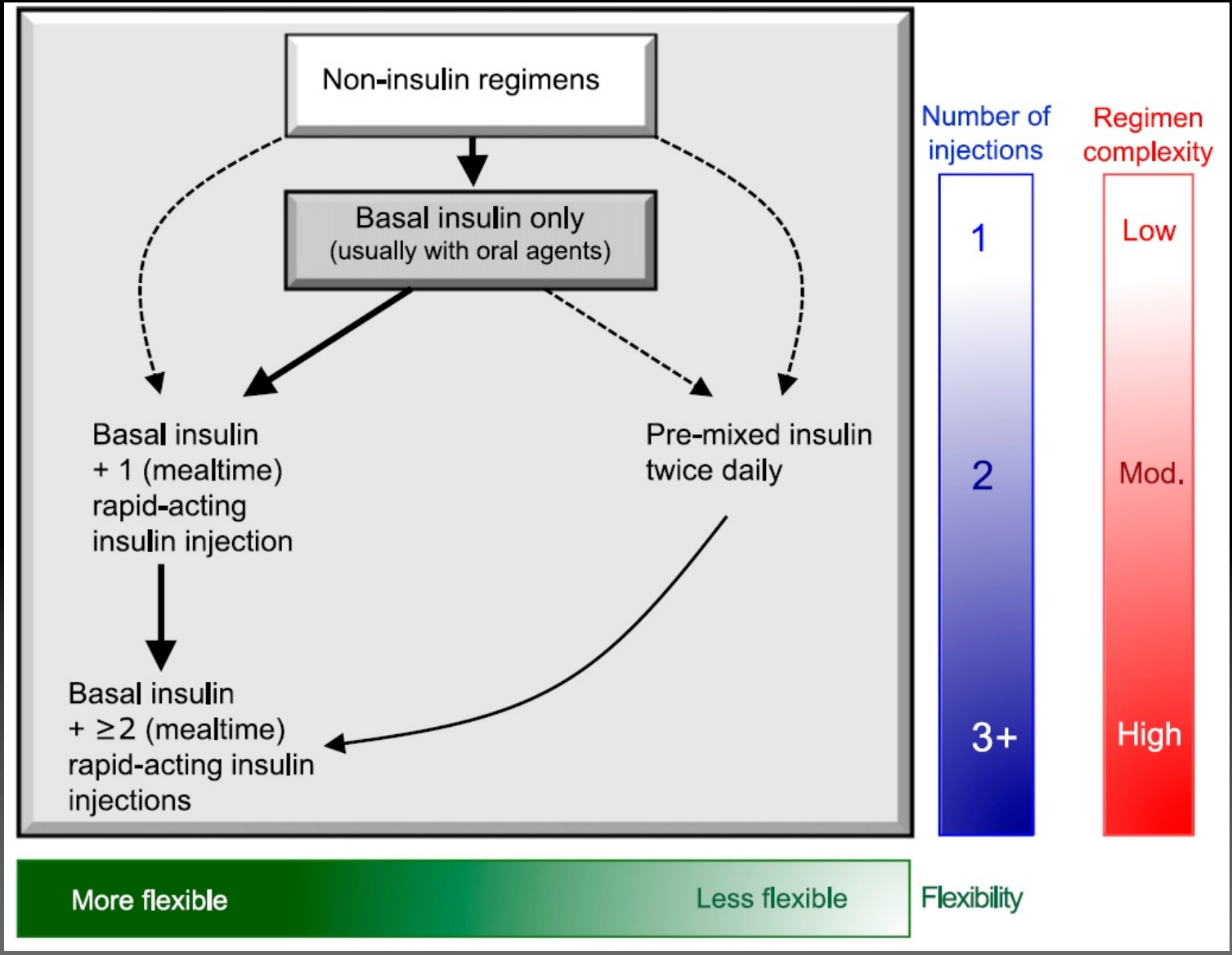
Lantus:

- Background insulin given morning or night with rapid acting insulin at biggest meal

PLUS

- Humalog, Apidra, Novorapid 3-6u at largest meal then up titrate depending on 2hr postprandial test

Sequential Insulin Strategies in T2D



Elderly

- Individualise HbA1c target (less evidence-based advice)
- Treat if hyperglycaemic symptoms
- Beware nocturnal hypo, i.e. morning NPH may be best esp if lunch biggest meal.

Renal Failure

- Often need to reduce insulin requirements as egfR drops below 25-30ml/min
- Watch for hypos

When to Stop Orals

- Usually continue METFORMIN in Type 2
- Stop sulphonylurea when prandial insulin started
- Usually stop pioglitazone when insulin is started (though Pio may reduce insulin requirement in some)

Follow-Up after Insulin Start

- Frequent at start with phone / email
- Most patients will progress to needing a short acting insulin so SMBG/HbA1c crucial to guide
- Diabetic Specialist Nurses will help at any stage
- Phone advice from Diabetes Specialist
- Insulin doses in overweight may easily exceed 1u/kg so important to regularly up titrate where necessary **and** review food and exercise regularly

Specialist Advice

If concerns and especially

- If patient may have Type I:
  - Rapid weight loss
  - Leaner
  - +ve GAD Ab
  - If significant symptoms with significant hyperglycaemia e.g. HbA1c >100 at diagnosis may need insulin to start and/or 1-2 oral agents
- Young patient < 25 years
- Vocational drivers
- Recurrent hypos
- If significant micro or macrovascular complications

Conclusion

- Set HbA1c target and negotiate with patient
- Review lifestyle
- Follow clinical pathway for oral agents
- Start insulin early if not meeting HbA1c targets
- Keep it safe and simple
- Ask for help if needed
- Treat BP & lipids according to guidelines