SEMI
SOCIEDAD ESPAÑOLA DE MEDICINA INTERNA
LA VISIÓN GLOBAL DE LA PERSONA ENFERMA

FEMI
FUNDACIÓN ESPAÑOLA DE MEDICINA INTERNA

Grupo de Diabetes y Obesidad

IX REUNIÓN DE DIABETES Y OBESIDAD

30-31 de Enero de 2015

FIBES - Palacio de Exposiciones y Congresos de Sevilla

IX REUNIÓN DE DIABETES Y OBESIDAD
30-31 de Enero de 2015 • FIBES - Palacio de Exposiciones y Congresos de Sevilla

"Facilitating the add-on moment for T2DM patients. What after metformin?"

ANDY COLLIER,
SCOTLAND

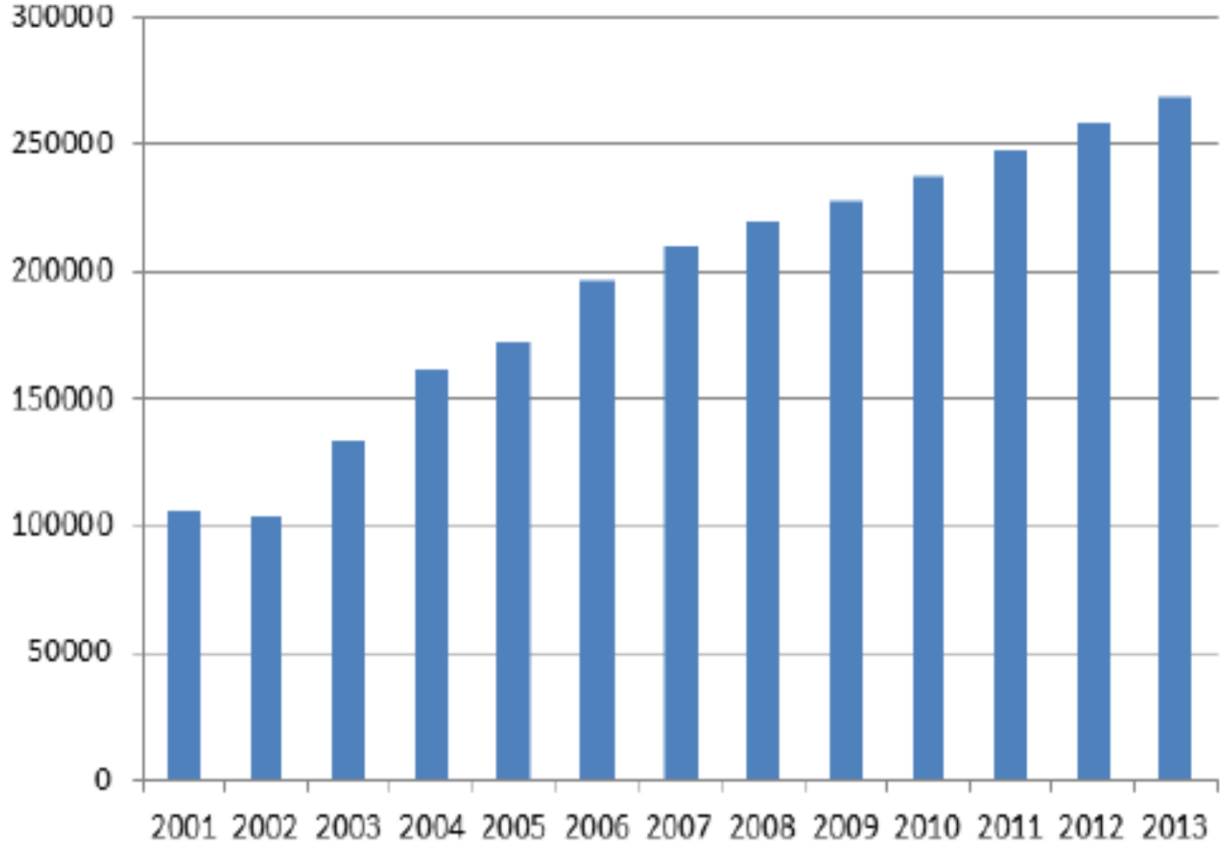

Shetland Islands (Scotland)
60°
2°
SCOTLAND
North Sea
Glasgow
Edinburgh
NORTHERN IRELAND
UNITED KINGDOM
Londonderry
Newcastle
Belfast
Isle of Man
Irish Sea
Leeds
Dublin
Liverpool
Manchester
Sheffield
Nottingham
IRELAND
Birmingham
ENGLAND
WALES
Cardiff
London
Bristol
Southampton
0 50 100 mi
0 50 100 km
FRANCE

University Hospital Ayr

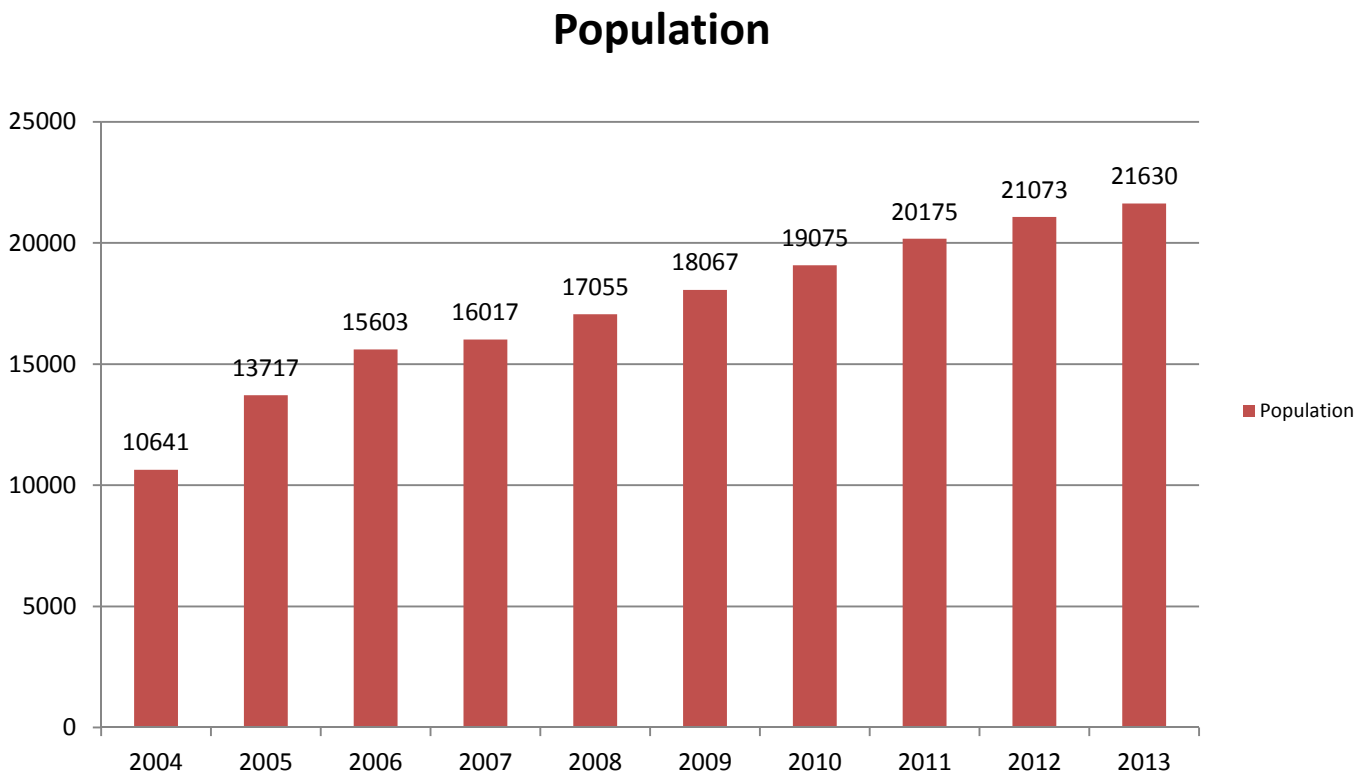
1984

Scotland 3
Spain 1

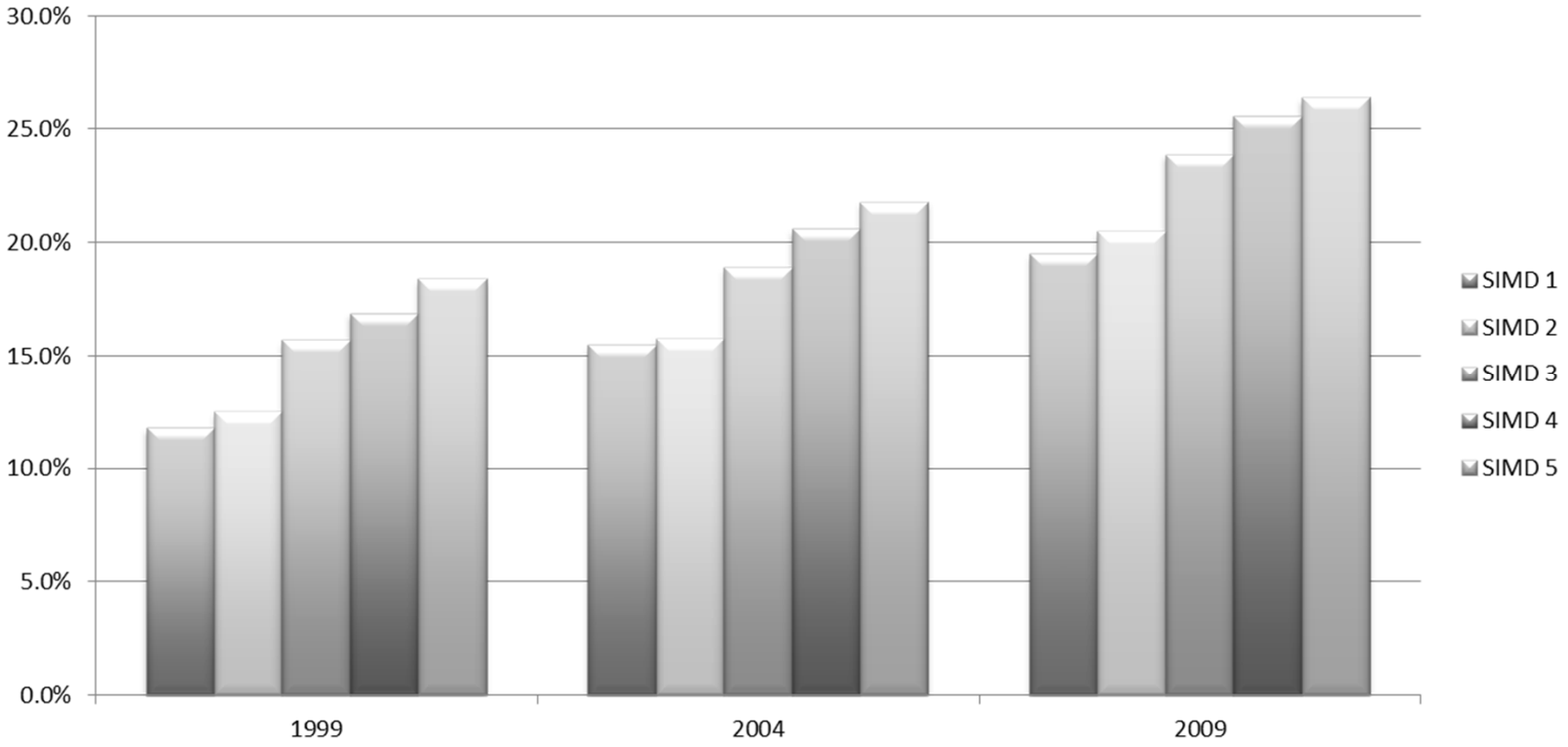
Diabetes in Scotland



Diabetes in Ayrshire and Arran



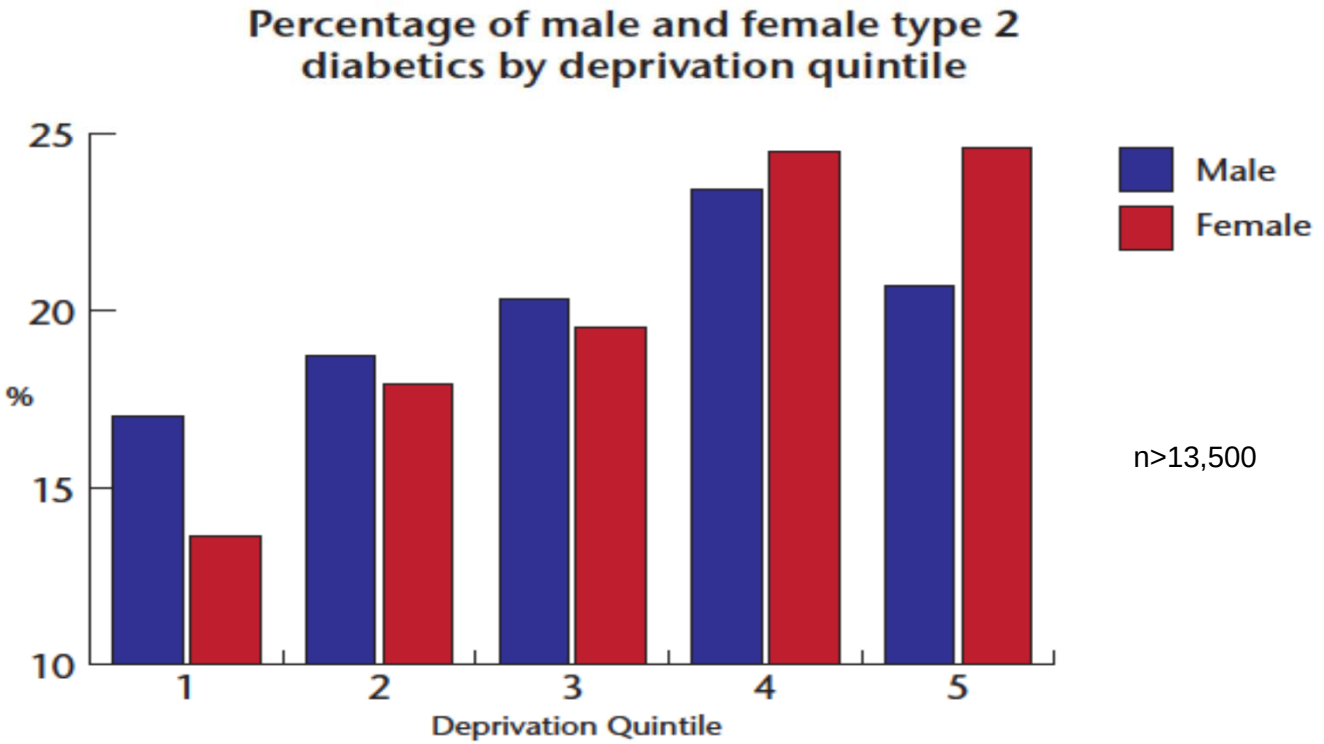
Obesity and deprivation in A&A



Mean BMI in A&A (2013)

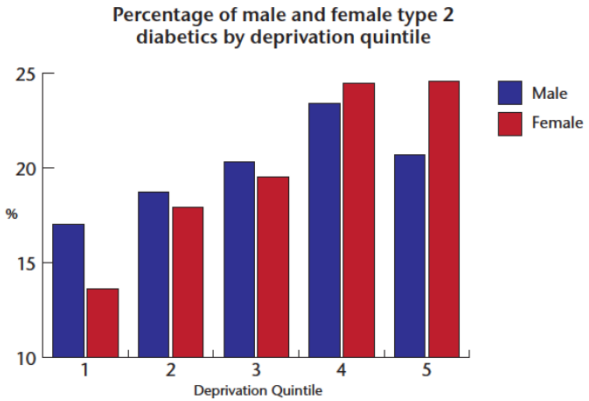
	Non-diabetes	Type 2 diabetes
Males	26.1 kg/m^2	31.4 kg/m^2
Females	26.9 kg/m^2	32.4 kg/m^2

Type 2 diabetes in A&A



n>13,500

Collier et al, 2014



- There was no association between glycaemic control and socioeconomic status (p = 0.12).

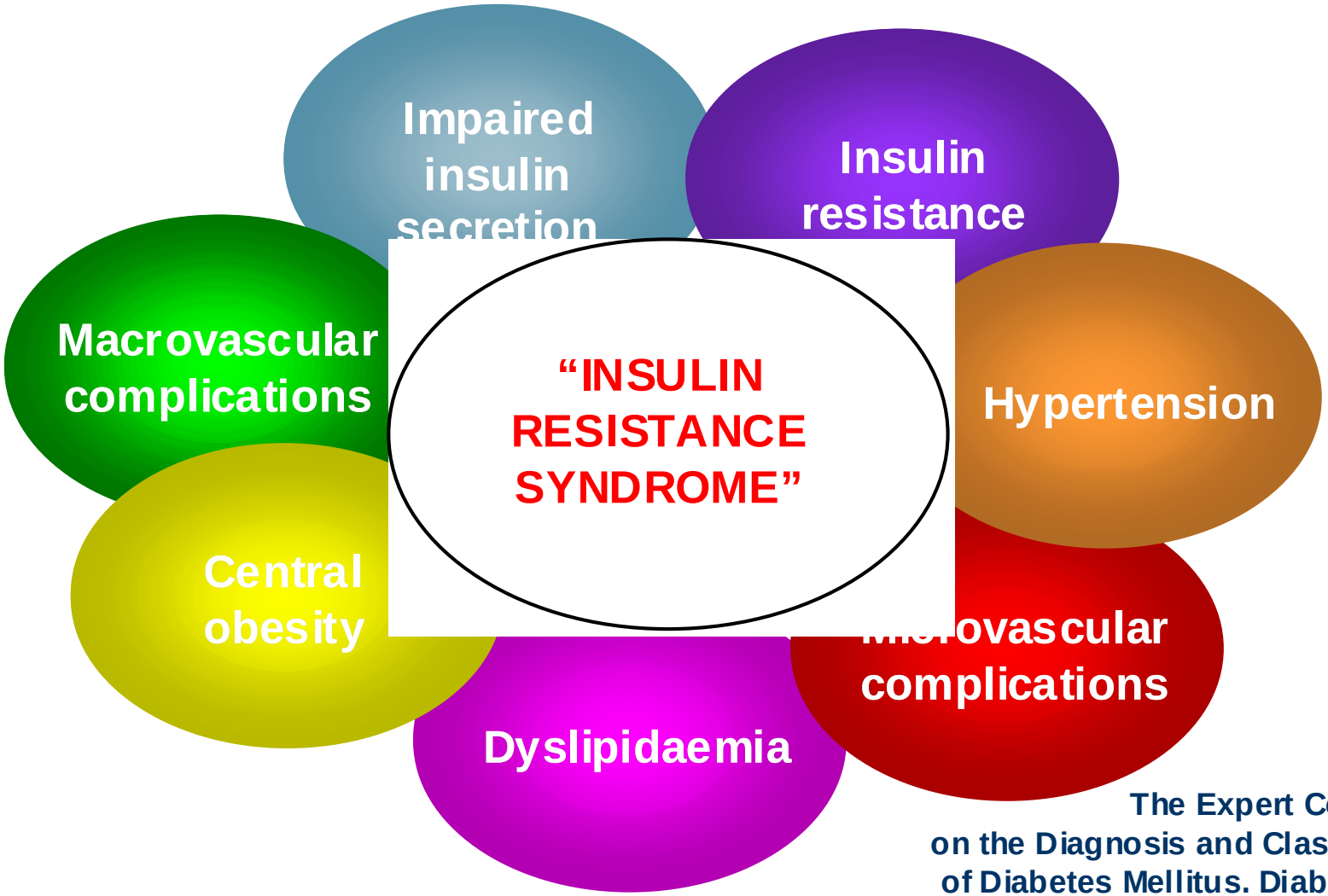
Collier et al, 2014

We know:

Type 2 diabetes

- Linked to obesity
- Obesity is becoming more prevalent
- Diabetes is becoming more prevalent
- Obesity and type 2 diabetes are linked to socioeconomic status.

Type 2 Diabetes:
A Complex Metabolic Disorder



The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; 20 (7): 1183–1203.

- diet & exercise/lifestyle change
- metformin
- combination of metformin + secretagogue
- more and more
  - triple oral therapy in patients
  - bedtime insulin + OHA
- multiple insulin injections + metformin (±pio/SGLT2i)

progressive β-cell failure

Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) June 2012

- "recommendations should be considered within the context of the needs, preferences, and tolerances of each patient; individualization of treatment is the cornerstone of success. Our recommendations are less prescriptive than and not as algorithmic as prior guidelines".

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ANTI-HYPERGLYCEMIC THERAPY

Glycemic targets

- **HbA1c < 7.0%** (8.3-8.9 mmol/l)
- Pre-prandial PG <7.2 mmol/l)
- Post-prandial PG <10.0 mmol/l
- **Individualization** is key:
  - Tighter targets (6.0 - 6.5%) - younger, healthier
  - Looser targets (7.5 - 8.0%+) - older, comorbidities, hypoglycemia prone, etc.
- Avoidance of hypoglycemia

1984

Assuming

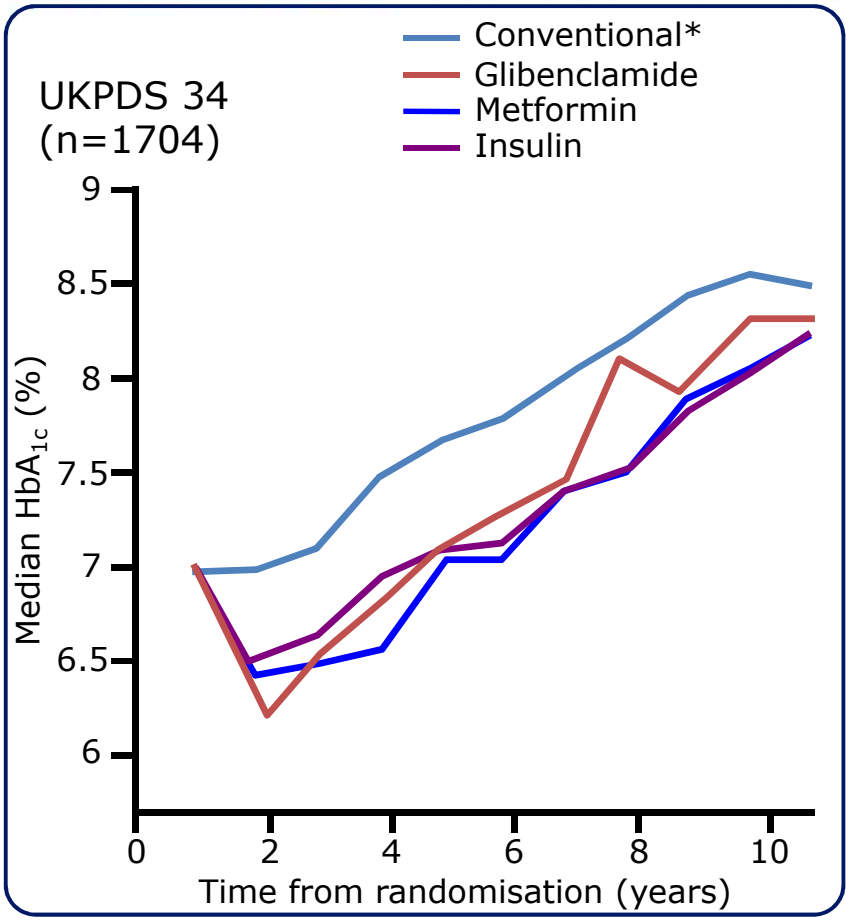
- Lifestyle advice
- Metformin as first line
- “start low, go slow”
- Better tolerance

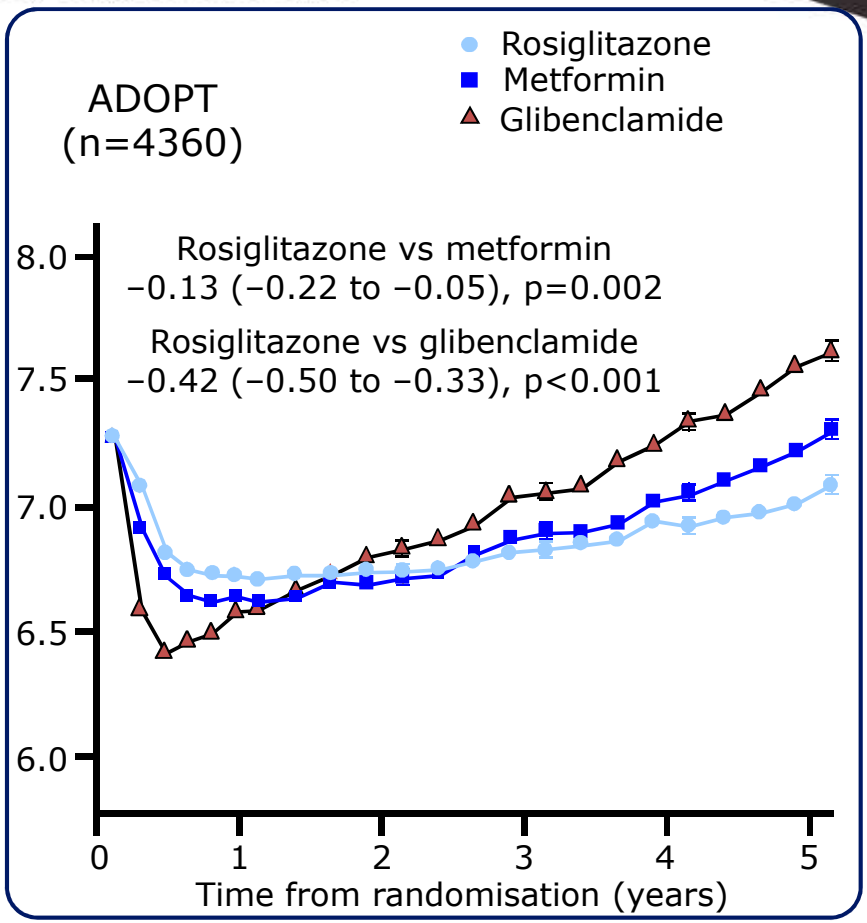
- → sulphonylurea (cost)

Why do we continue to use a class of drugs?

Sulfonylureas

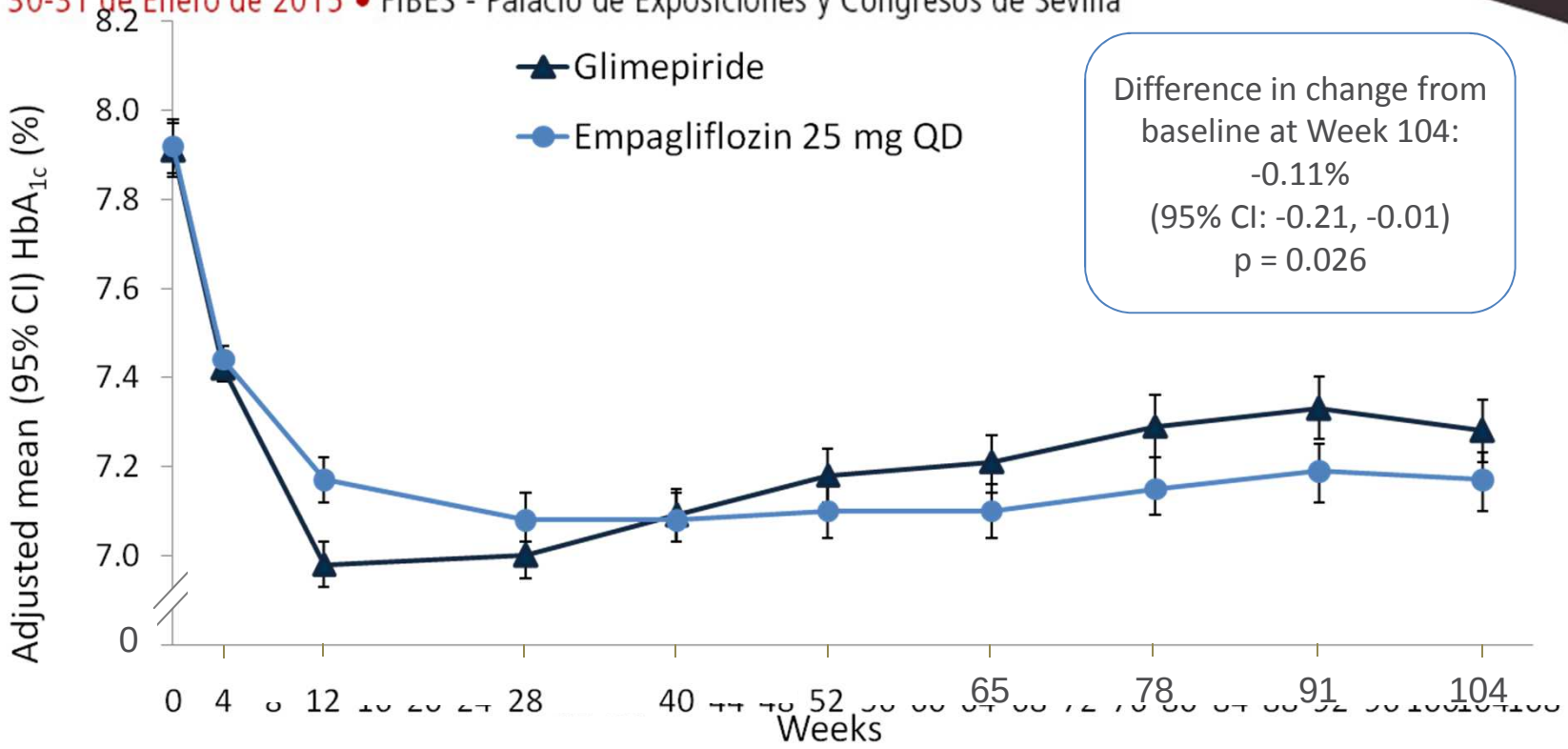
- Lead to further weight gain
- Efficacy falls away





*Diet initially then sulphonylureas, insulin and/or metformin if fasting plasma glucose >15 mmol/L

Over time, glycaemic control deteriorates.



Analysed patients

Glimepiride	761	758	738	699	660	609	562	524	494	461
Empagliflozin	759	751	734	702	672	646	624	593	568	548

Empagliflozin versus glimepiride change in HbA_{1c}

CI, confidence interval; H2H, head-to-head; HbA_{1c}, glycosylated haemoglobin; QD, once daily.
MMRM. FAS (OC).
Ridderstråle M, et al. *Lancet Diabetes Endocrinol.* 2014;2:691–700.

Why do we use a drug?

- Leads to further weight gain
- Efficacy falls away
- Gliclazide – too large a dose!
- Contentious cardiovascular data (UGDP-1971)
- Increases the risk of hypoglycaemia
- Downstream costs are high
- Increases patients risk of needing to go onto insulin.

Diabetes Prescribing Strategy 2014 to 2016 (Scotland)

Sulfonylureas:

- “recognised as second-line agents in patients who are not overweight “
- “first-line agent for those who are intolerant of, or have contra-indications to, metformin”
- “reduce clinically important microvascular complications”
- “they remain the least expensive second line agent”
- >70% of type 2 patients on MF + SU

Diabetes Prescribing Strategy 2014 to 2016

- “Self Blood Glucose Monitoring (SBGM) is not suitable or recommended for all those with type 2 diabetes”
- “there are clear recommendations for specific groups of patients. SBGM is essential for people with type 2 diabetes……
- who are at risk of hypoglycaemia due to sulfonylurea”.

Diabetes Prescribing Strategy 2014 to 2016

- Cheap drug
- Self Blood Glucose Monitoring

a. Expensive
b. Quality of life
c. Patient satisfaction
d. Anxiety scores

ANTI-HYPERGLYCEMIC THERAPY

Therapeutic options:

Oral agents & non-insulin injectables

- **Metformin**
- **Sulfonylureas**
- **Thiazolidinediones**
- **DPP-4 inhibitors**
- **SGLT-2 inhibitors**
- **Meglitinides**
- **α-glucosidase inhibitors**
- **Bile acid sequestrants**
- **Dopamine-2 agonists**
- **Amylin mimetics**

ANTI-HYPERGLYCEMIC THERAPY

Therapeutic options:

Oral agents & non-insulin injectables

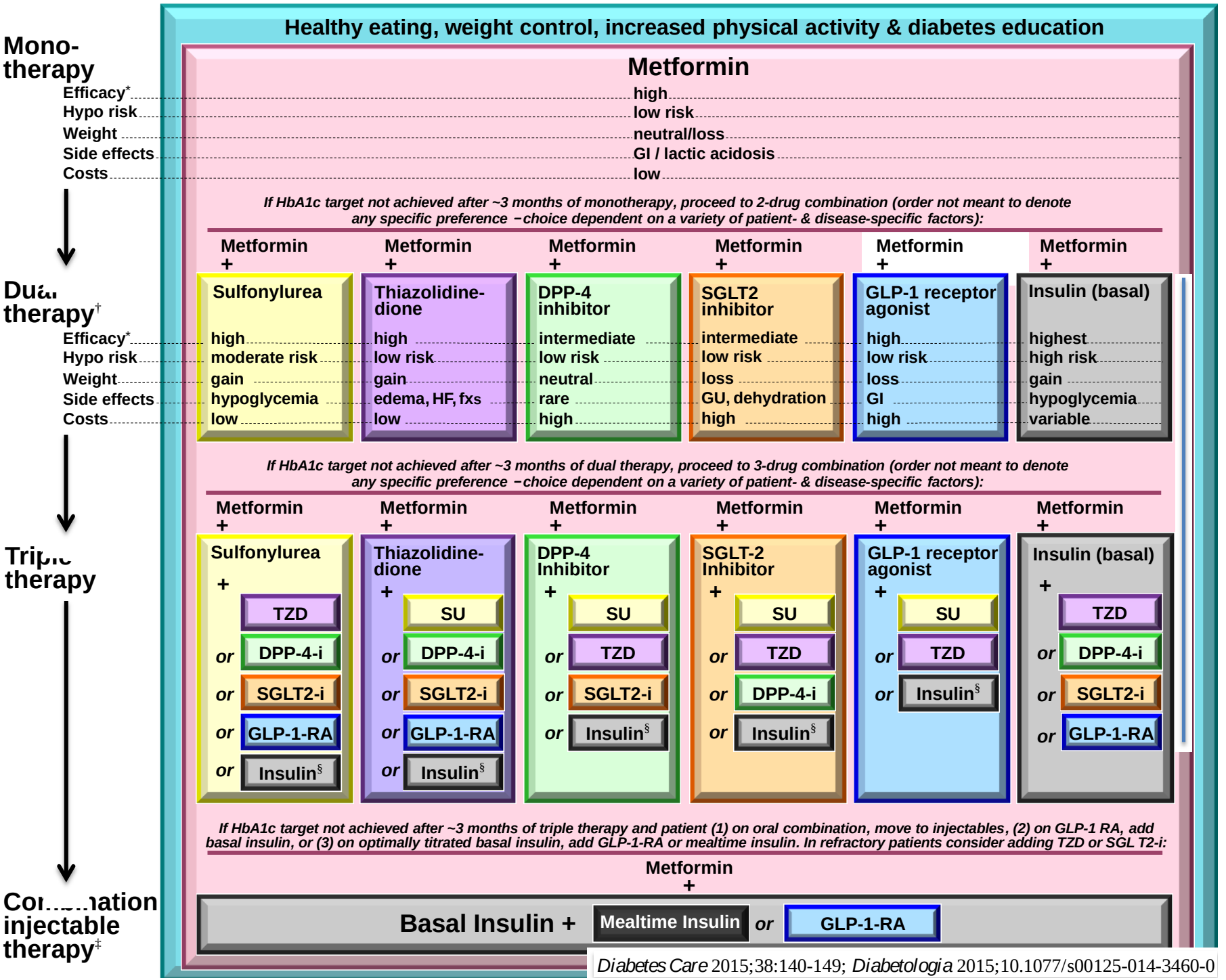
Metformin

Sulfonylureas

Thiazolidinediones

DPP-4 inhibitors

SGLT-2 inhibitors



Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0

Class	Mechanism	Advantages	Disadvantages
Biguanides (Metformin)	• Activates AMP-kinase • ↓ Hepatic glucose production	• Extensive experience • No hypoglycemia • Weight neutral • ? ↓ CVD events	• Gastrointestinal • Lactic acidosis • B-12 deficiency • Contraindications
SUs / Meglitinides	• Closes KATP channels • ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk	• Hypoglycemia • Weight gain • Low durability • ? ↓ Ischemic preconditioning
TZDs	• Activates PPAR-γ • ↑ Insulin sensitivity	• No hypoglycemia • Durability • ↓ TGs, ↑ HDL-C • ? ↓ CVD events (pio)	• Weight gain • Edema / heart failure • Bone fractures • ? ↑ MI (rosi) • ? Bladder ca (pio)

***Diabetes Care* 2015**
***Diabetologia* 2015**

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***Diabetes Care* 2015**
***Diabetologia* 2015**

Class	Mechanism	Advantages	Disadvantages
DPP-4 inhibitors	• Inhibits DPP-4 • Increases GLP-1, GIP	• No hypoglycemia • Well tolerated	• Modest ↓ A1c • ? Pancreatitis • Urticaria
GLP-1 receptor agonists	• Activates GLP-1 receptor • ↑ Insulin, ↓ glucagon • ↓ gastric emptying • ↑ satiety	• Weight loss • No hypoglycemia • ? ↑ Beta cell mass • ? CV protection	• GI • ? Pancreatitis • Medullary ca • Injectable 
SGLT-2 inhibitors	•Inhibits SGLT2 in proximal tubule •Increases glycosuria	•↓weight •No hypoglycaemia •↓blood pressure •Effective at all stages	•GU infections •Polyurria •Volume depletion •↑LDL-chol •↑Creat (transient)

***Diabetes Care* 2015**
***Diabetologia* 2015**

Class	Mechanism	Advantages	Disadvantages
DPP-4 inhibitors	• **Inhibits DPP-4** • **Increases GLP-1,** GIP	• **No hypoglycemia** • **Well tolerated**	• **Modest ↓ A1c** • ? Pancreatitis • Urticaria
GLP-1 receptor agonists	• **Activates GLP-1 receptor** • **↑ Insulin, ↓ glucagon** • **↓ gastric emptying** • **↑ satiety**	• **Weight loss** • **No hypoglycemia** • ? ↑ Beta cell mass • ? CV protection	• **GI** • ? Pancreatitis • Medullary ca • **Injectable** 
SGLT-2 inhibitors	•**Inhibits SGLT2 in proximal tubule** •**Increases glycosuria**	•**↓weight** •**No hypoglycaemia** •**↓blood pressure** •**Effective at all stages**	•**GU infections** •**Polyurria** •Volume depletion •↑LDL-chol •↑Creat (transient)

***Diabetes Care* 2015**
***Diabetologia* 2015**

Class	Mechanism	Advantages	Disadvantages
Insulin	• Activates insulin receptor • ↑ Glucose disposal • ↓ Hepatic glucose production	• Universally effective • Unlimited efficacy • ↓ Microvascular risk	• Hypoglycemia • Weight gain • ? Mitogenicity • Injectable • Training requirements • "Stigma"

***Diabetes Care* 2015**
***Diabetologia* 2015**

Class	Mechanism	Advantages	Disadvantages
Insulin	• **Activates insulin receptor** • **↑ Glucose disposal** • **↓ Hepatic glucose production**	• **Universally effective** • **Unlimited efficacy** • **↓ Microvascular risk**	• **Hypoglycemia** • **Weight gain** • ? Mitogenicity • **Injectable** • **Training requirements** • **"Stigma"**

***Diabetes Care* 2015**
***Diabetologia* 2015**

Type 2 diabetes

- progressive disease
- ß-cell failure
- development of complications
- medications at diagnosis
- medications later in disease process
- co-morbidities.

Comorbidities

- **Coronary Disease**
- **Heart Failure**
- **Renal disease**
- **Liver dysfunction**
- **Hypoglycemia**

- Metformin: CVD benefit (UKPDS)
- Avoid hypoglycemia
- ? SUs & ischemic preconditioning
- ? Pioglitazone & ↓ CVD events
- ? Effects of incretin-based therapies

Comorbidities

- **Coronary Disease**
- **Heart Failure**
- **Renal disease**
- **Liver dysfunction**
- **Hypoglycemia**

- Metformin: May use unless condition is unstable or severe
- Avoid TZDs
- ? Effects of incretin-based therapies

Comorbidities

- **Coronary Disease**
- **Heart Failure**
- **Renal disease**
- **Liver dysfunction**
- **Hypoglycemia**

- Increased risk of hypoglycemia
- Metformin & lactic acidosis
  - US: stop @SCr ≥ 1.5 (1.4 women)
  - UK: half-dose @GFR < 45 & stop @GFR < 30
- Caution with SUs (esp. glibenclamide)
- DPP-4-i's – dose adjust for most (not linagliptin)
- Avoid exenatide if GFR < 30
- SGLT2 inhibitors @GFR < 60

Comorbidities

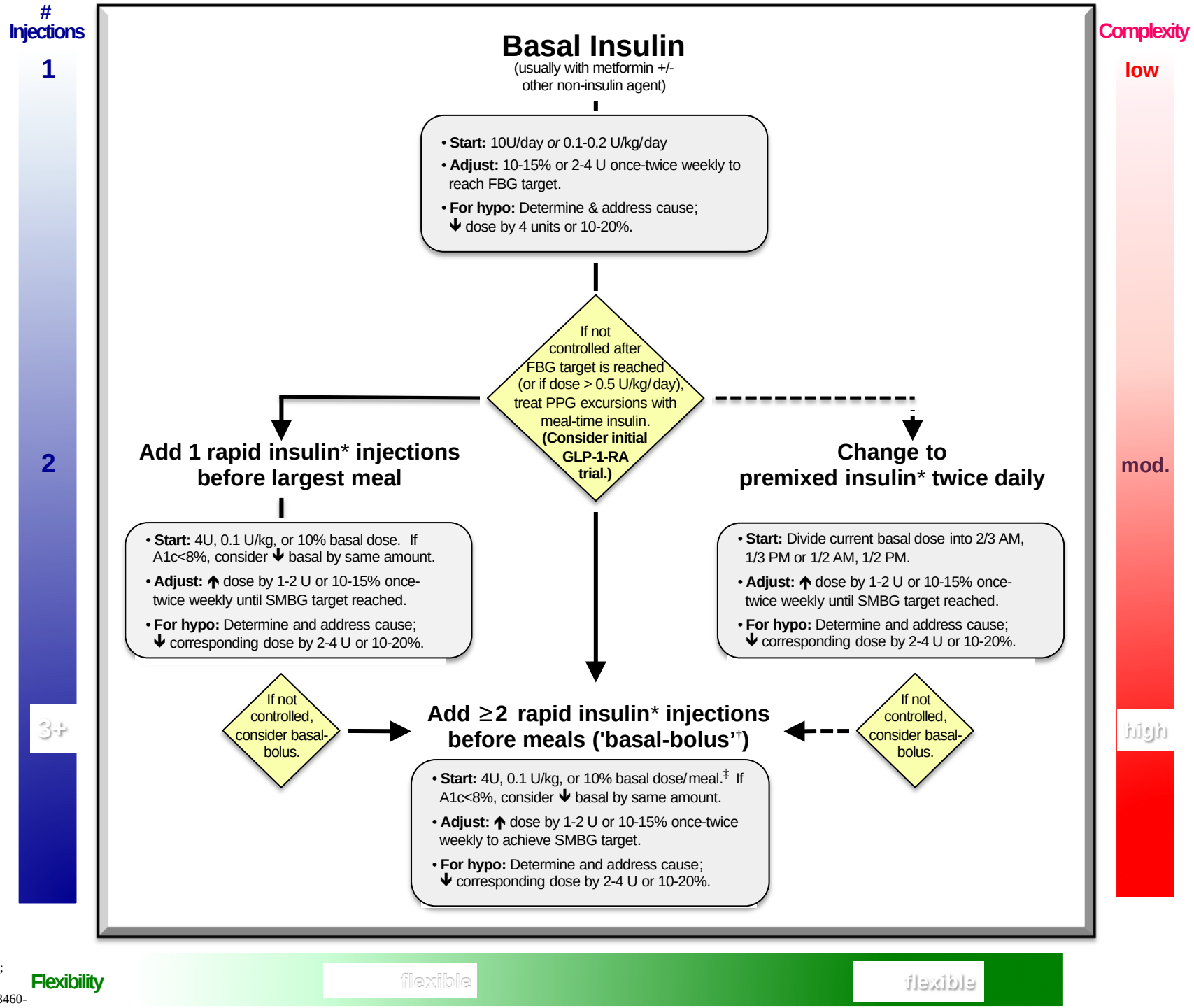
- **Coronary Disease**
- **Heart Failure**
- **Renal disease**
- **Liver dysfunction**
- **Hypoglycemia**

- Most drugs not tested in advanced liver disease
- Pioglitazone may help steatosis
- Insulin best option if disease severe

Comorbidities

- **Coronary Disease**
- **Heart Failure**
- **Renal disease**
- **Liver dysfunction**
- **Hypoglycemia**

- Emerging concerns regarding association with increased morbidity / mortality
- Proper drug selection is key in the hypoglycemia prone



Diabetes Care 2015;38:140;
Diabetologia 2015;10.1077/s00125-014-3460-

- **Two clinical cases**

Busy, active mother of three
Age: 45

- Office administrator
- Diagnosed with type 2 diabetes three years ago
- Drives to work and 'ferries' children every day
- Attended a structured education programme last year

- Joined a slimming club but still struggling to find time to plan healthier meals that the whole family will eat
- Hesitant to take add-on therapy - *"I'm very young to be on all these medications"*

- Weight gain over last 2 years - BMI: 29 kg/m^2
- BP: 132/83 mmHg
- HbA_{1c}: 8.1%
- Normal renal function

- Currently on metformin: 1 g bd (the maximum dose tolerated, adherence confirmed)

Busy, active mother of three
Age: 45

Management review

- HbA_{1c} 8.1% - requires additional control
- Attended structured education programme last year
- Struggling to improve diet
- Recent weight gain

Treatment options

- A sulphonylurea (e.g. gliclazide)
- A DPP-4 inhibitor (gliptin)
- A thiazolidinedione (glitazone)
- An SGLT2 inhibitor
- A GLP-1 agonist
- Basal insulin

45 years old

- Further lifestyle advice
- Gliclazide 80 → 160 mgs twice daily

48 years old – 3 years later

- 5kgs heavier
- BMI>30kg/m^2
- HbA_{1c} 8.6%

Treatment options

- A DPP-4 inhibitor (gliptin)
- A thiazolidinedione (glitazone)
- An SGLT2 inhibitor
- A GLP-1 agonist
- Basal insulin

48 years old – 3 years later

- Reduce or stop gliclazide
- Gliptin
- SGLT2 inhibitor
- Pioglitazone
- (GLP1 analogue)

- Reinforce lifestyle advice
- Cardiovascular risk factors
- Insulin therapy

A.S. 59 year old male

Travelling salesman – driving every day

Diet is poor and sporadic

Diagnosed with type 2 diabetes three years ago

Offered structured education programme and declined

Recently cut his work hours and general activity due to ill health, consequently gained weight

A smoker: concerned about further weight gain if he gives up smoking

Co-morbidity: COPD (managed with appropriate inhalers)

BMI: 36 kg/m^2

BP: 136/78 mmHg

HbA_{1c}: 8.9%

eGFR: normal

“does not want injections”

Currently on metformin 1 g bd (the maximum dose tolerated)

A.S. 59 year old male

Lifestyle advice

- Smoking cessation programme enrolment
- Participation in structured education ‘refresher’
- Driving is part of his business

Treatment options

- A sulphonylurea (e.g. gliclazide)
- Gliptin
- Pioglitazone
- An SGLT2 inhibitor
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- Basal insulin

A.S. 59 year old male

- Reinforce lifestyle advice
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Treatment options

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KEY POINTS

- Glycemic targets & BG-lowering therapies must be individualized.
- Diet, exercise, & education: foundation of any T2DM therapy program
- Unless contraindicated, metformin = optimal 1st-line drug - “start low, go slow”.
- Progressive disease:
  ß-cell failure
  increased weight → further insulin resistance
  development of complications
  impact on management

KEY POINTS

- After metformin, data are limited. Combination therapy with 1-2 other oral / injectable agents is reasonable; minimize side effects.
- Ultimately, many patients will require insulin therapy alone / in combination with other agents to maintain BG control.
- All treatment decisions should be made in conjunction with the patient (focus on preferences, needs & values.)
- Comprehensive CV risk reduction - a major focus of therapy.

- **Thank you**
- **Any questions?**

What I do

At diagnosis

- Tight control
- Metformin
- Gliclazide (80mg twice daily as maximum/stop after a few weeks)

What I do

At diagnosis

- Tight control
- Metformin
- [Gliclazide (80mg twice daily as maximum/stop after a few weeks)]
- DPP-4-i's
- SGLT2 inhibitor
- Pioglitazone
- If BMI>35 kg/m^2 – GLP1 inhibitor

What I do

At diagnosis

- Tight control
- Metformin
- [Gliclazide (80mg twice daily as maximum/stop after a few weeks)]
- DPP-4-i's
- SGLT2 inhibitor
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- If BMI>35 kg/m^2 – GLP1 inhibitor

10-15 yrs into diagnosis

- Less tight control
- Metformin
- Reduce or stop gliclazide
- DPPIV I

What I do

At diagnosis

- Tight control
- Metformin
- [Gliclazide (80mg twice daily as maximum/stop after a few weeks)]
- DPP-4-i's
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