Type 2 Diabetes – Effective Management

A/Prof Sof Andrikopoulos

CEO

Australian Diabetes Society

National Diabetes Services Scheme

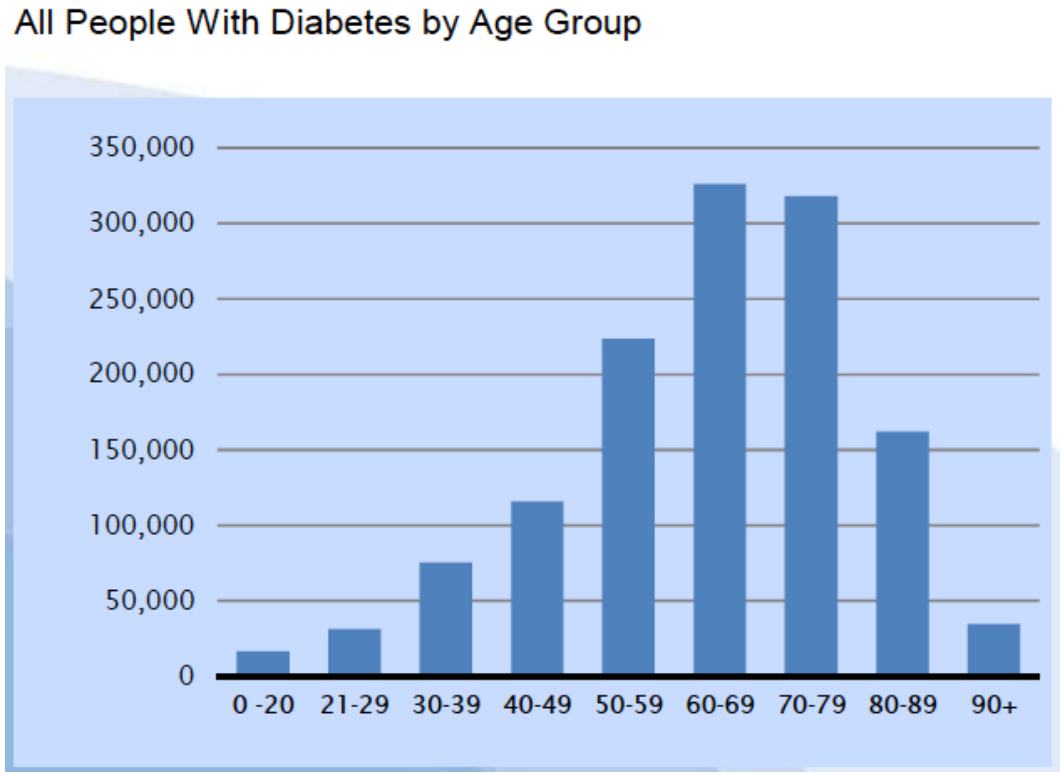
as at 31 March 2019

There were 1,302,303 people with diabetes registered with the NDSS

Diabetes Type	Number	%	Registered in Past Year
Type 1	119,751	9%	3,360
Type 2	1,132,318	87%	60,162
Gestational*	41,508	3%	41,508
Other	8,726	< 1%	1,150
Total	1,302,303	100%	106,180

* An additional 165,780 women who previously had gestational diabetes are registered with the NDSS. These women are at high risk of developing type 2 diabetes and receive regular reminder letters to have a diabetes check.

National Diabetes Services Scheme



8,493 people with diabetes were aged 15 years or under

16,633 people with diabetes were aged 20 years or under

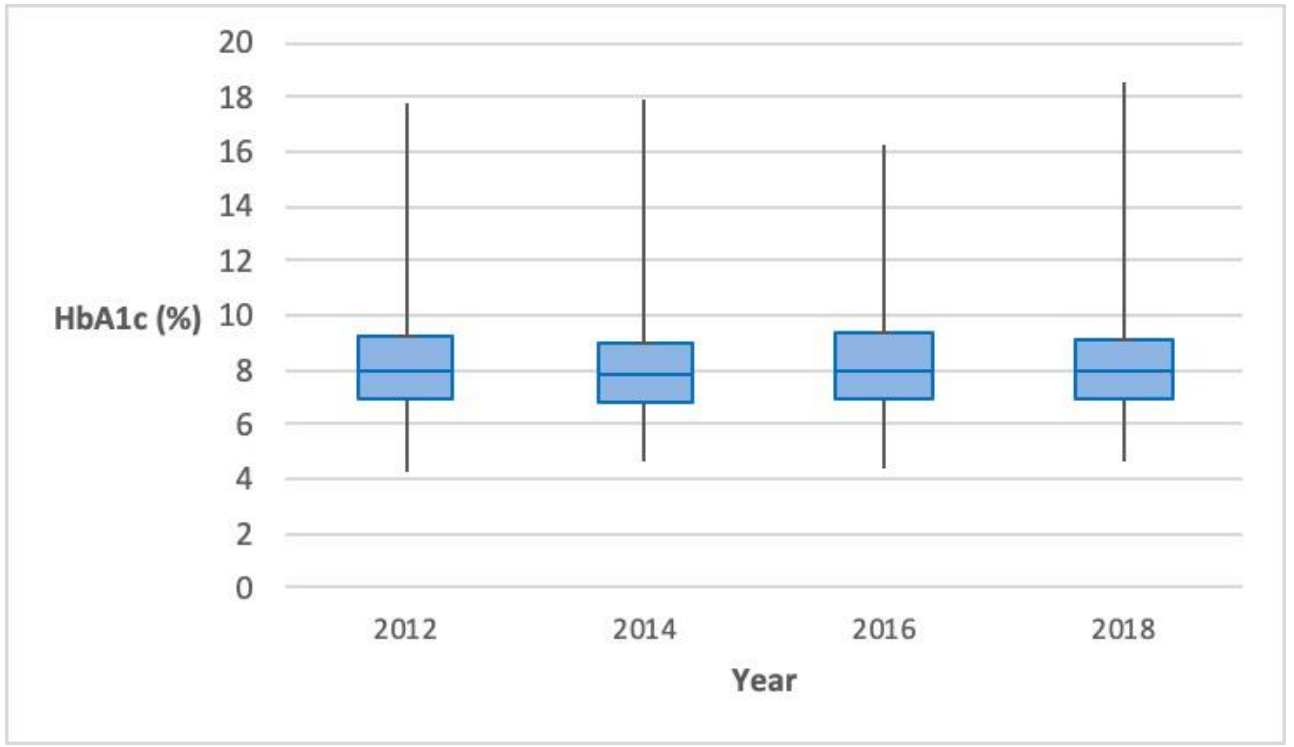
31,394 people with diabetes were aged 21 to 29 years old

75,198 people with diabetes were aged 30 to 39 years old

840,142 people with diabetes were aged 60 years or older

Australian National Diabetes Audit (ANDA-AQCA) HbA1c Results 2018

Figure 9 - Glycaemic control in patients with type 2 diabetes



Diabetes Discovery Initiative – Austin Health

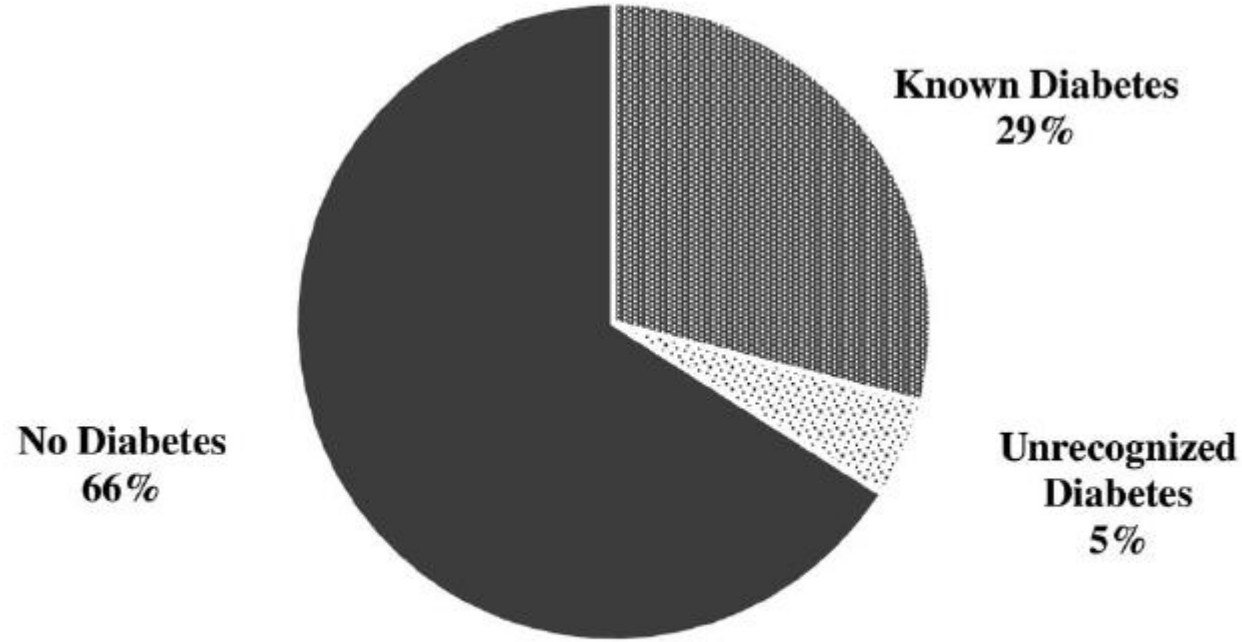
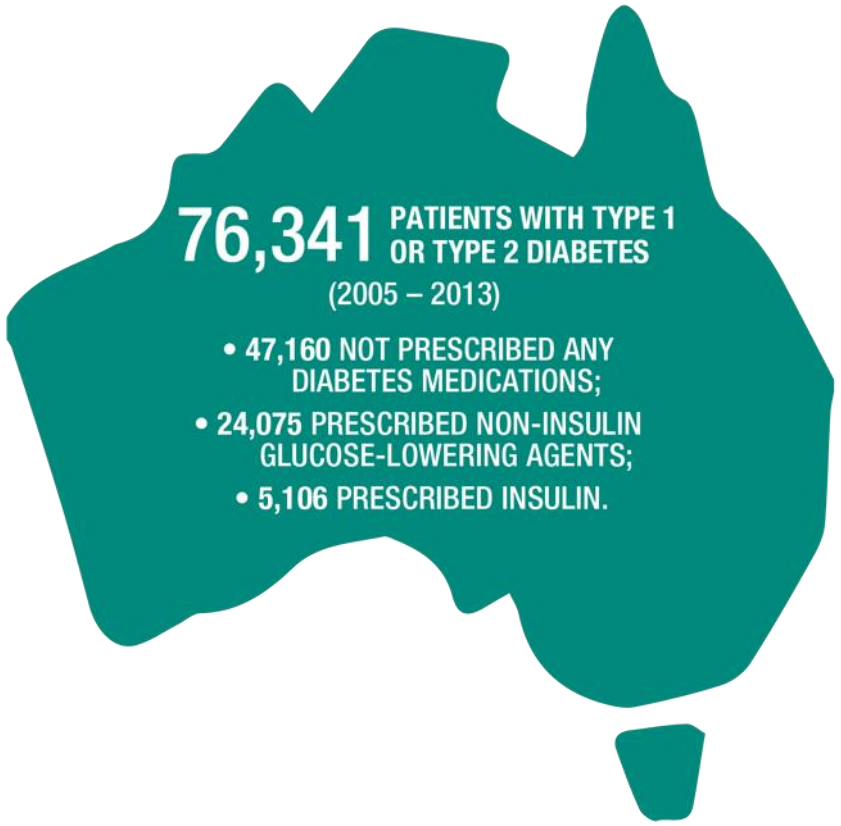


Figure 3 The prevalence of known, unrecognized and no diabetes in inpatients ≥54 years.

Nanayakkara et al. BMJ Open Diabetes Res Care 2015

How are we doing with glycaemic control?



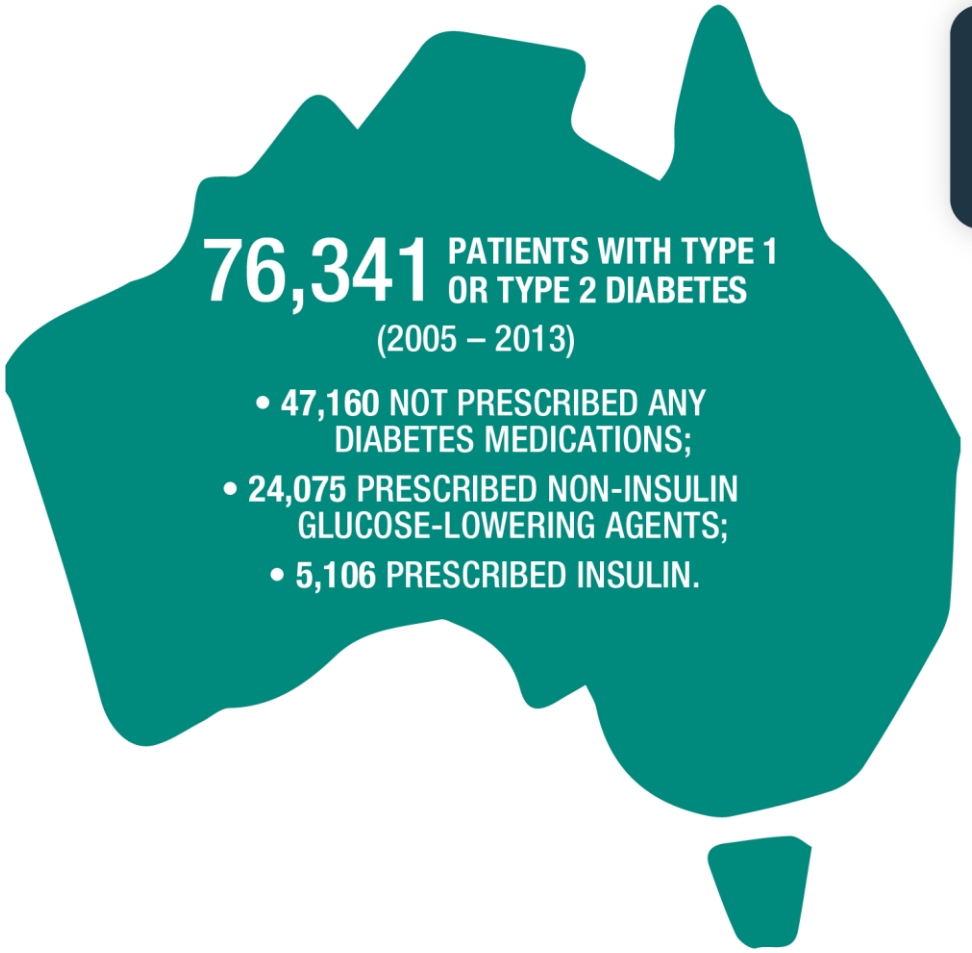
In 2013, the percentage who did not achieve glycaemic control <7% (53 mmol/mol):

- **15%** of individuals not prescribed any diabetes medications
- **47%** of individuals prescribed non-insulin glucose-lowering agents
- **75%** of individuals prescribed insulin.

This study analysed 275,480 HbA1c results (from 76,341 patients) and glucose-lowering prescription records from a medical database during 2005–2013 to examine trends in blood glucose levels and glycaemic control, and estimate avoidable glycaemic burden in Australian primary care.

Carrington MJ *et al. Diabetes Res Clin Prac* 2017; 127:89–96.

Treatment inertia is a real issue



Time with a HbA1c ≥7%

9 MONTHS in individuals **not prescribed** any diabetes medications

15-16 MONTHS in individuals **prescribed non-insulin** glucose-lowering agents

18-27 MONTHS in individuals **prescribed insulin**

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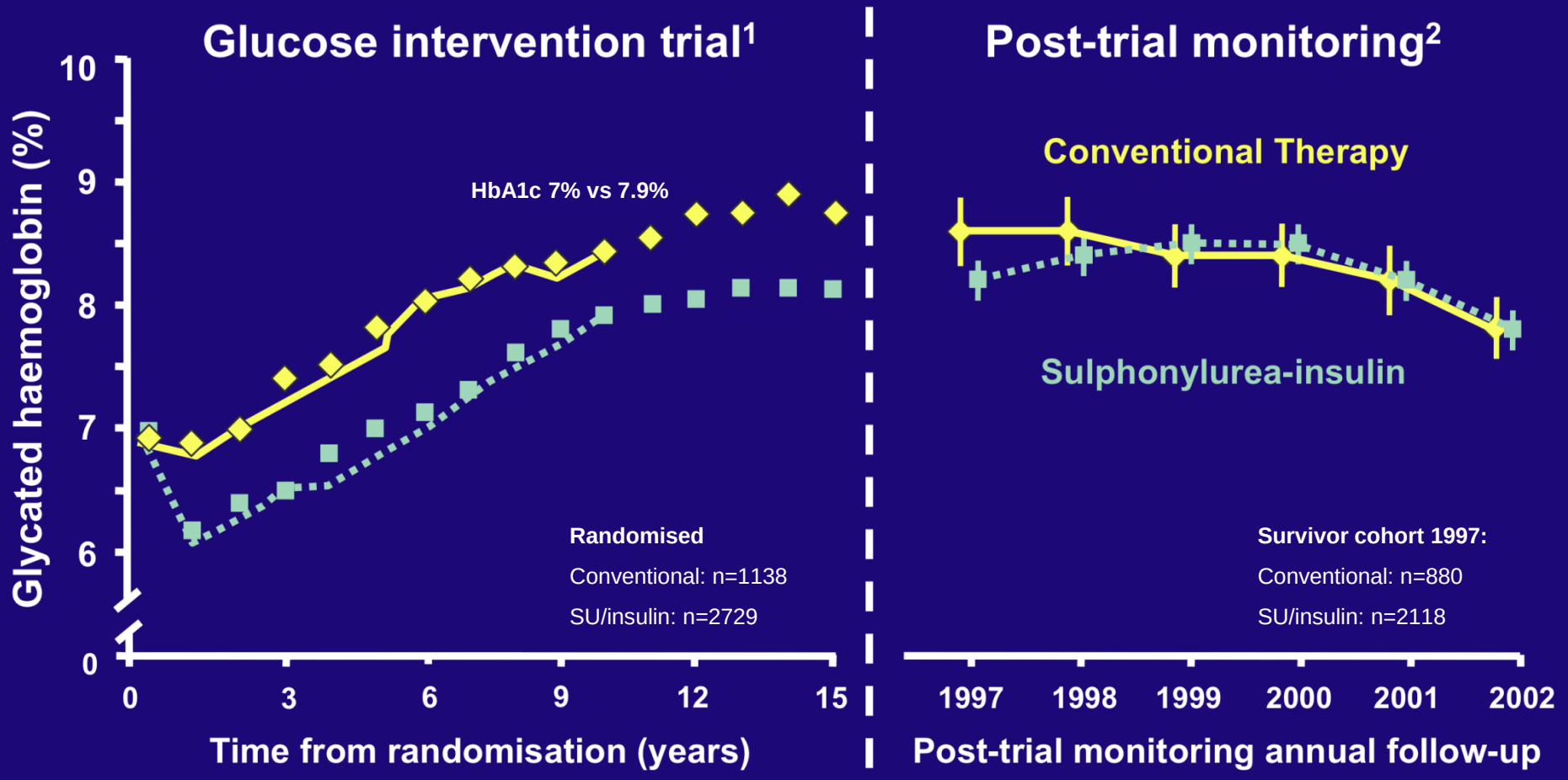
UKPDS post-trial follow-up: differences in HbA_{1c} were not maintained after RCT ceased



Glucose intervention trial

Patients followed for 10 years:

All patients designated to regimen:

[1]UKPDS Group. *Lancet* 1998;352:837–853.
[2]Holman R, *et al. N Engl J Med* 2008;359:1577–1589.

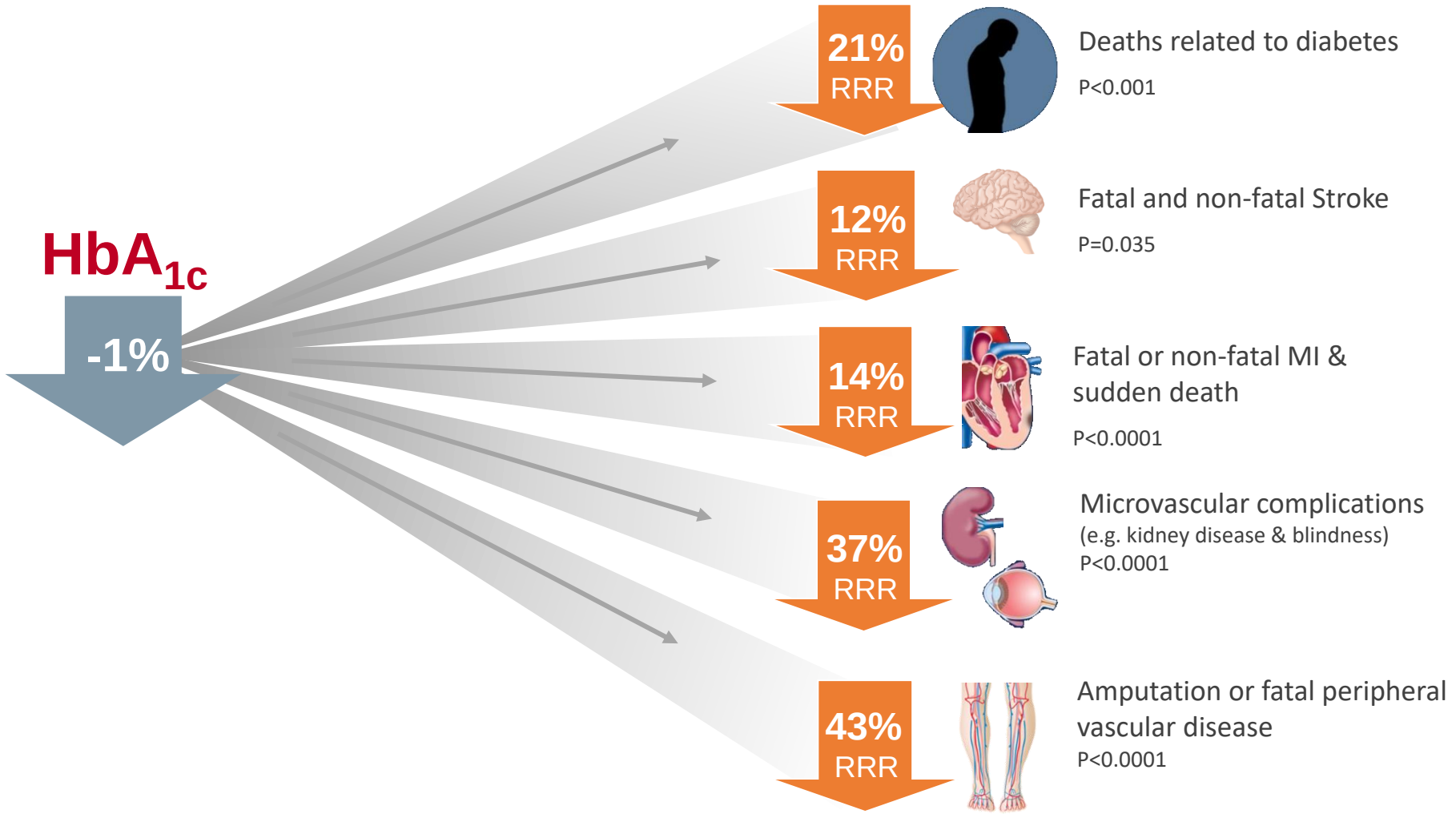
UKPDS: legacy effect of earlier glucose control

		End of randomised intervention[1] 1997	End of 10-year observational follow-up[2] 2007
Any diabetes related endpoint	RRR p-value	12% 0.029	9% 0.040
Microvascular disease	RRR p-value	25% 0.0099	24% 0.001
Myocardial infarction	RRR p-value	16% 0.052	15% 0.014
All-cause mortality	RRR p-value	6% 0.44	13% 0.007

RRR = relative risk reduction associated with intensive glucose control

[1]UKPDS Group. *Lancet* 1998;352:837–853.
[2]Holman R, *et al. N Engl J Med* 2008;359:1577–1589.

The benefit of a 1% reduction in HbA1c



UKPDS (35): Stratton IM, *et al*. *BMJ.* 2000;321(7258):405-412.

DIABETICMedicine

HbA_{1c} 3 months after diagnosis predicts premature mortality in patients with new onset type 2 diabetes

- 3,781 new onset T2D patients referred between 1999-2003
- Determine which factors contributed significantly to 5 year mortality rates- age at diagnosis, HbA1c achieved at 3 months, smoking, BP, gender, BMI, lipids

Factor	At risk	Deaths	Unadjusted HR (a)	95% CI	Adjusted for age HR (b)	95% CI	Final model HR (c)*	95% CI
HbA_{1c} % (mmol/mol) at 3 months								
< 6.5 (48) (Reference)	650	65	1.0		1.0		1.0	
6.4–7.4 (48–57)	1141	175	1.3	1.0–1.8	1.1	0.9–1.5	1.1	0.8–1.4
7.5–8.4 (58–68)	563	132	1.8	1.4–2.5	1.6	1.2–2.2	1.5	1.1–2.1
8.5 + (69)	328	80	1.9	1.4–2.7	2.0	1.5–2.8	1.6	1.1–2.3
P			< 0.001		< 0.001		< 0.001	

** After adjusting for age, BMI, lipids, BP, smoking history and gender*

Conclusion: "…It may be appropriate to consider early and intensive intervention for individuals with new onset type 2 diabetes."

D. Kerr, et al, Diabetic Medicine 2011. DOI:10.1111/j.1464-5491.2011.03443.x

Metabolic memory: good metabolic control early prevents complications later

Salvatore Dali La persistència de la memòria 1931 MOMA, New York

What's holding us back?

Proportion of Australian T2D patients with HbA1c >7%

Physician or Clinical Inertia

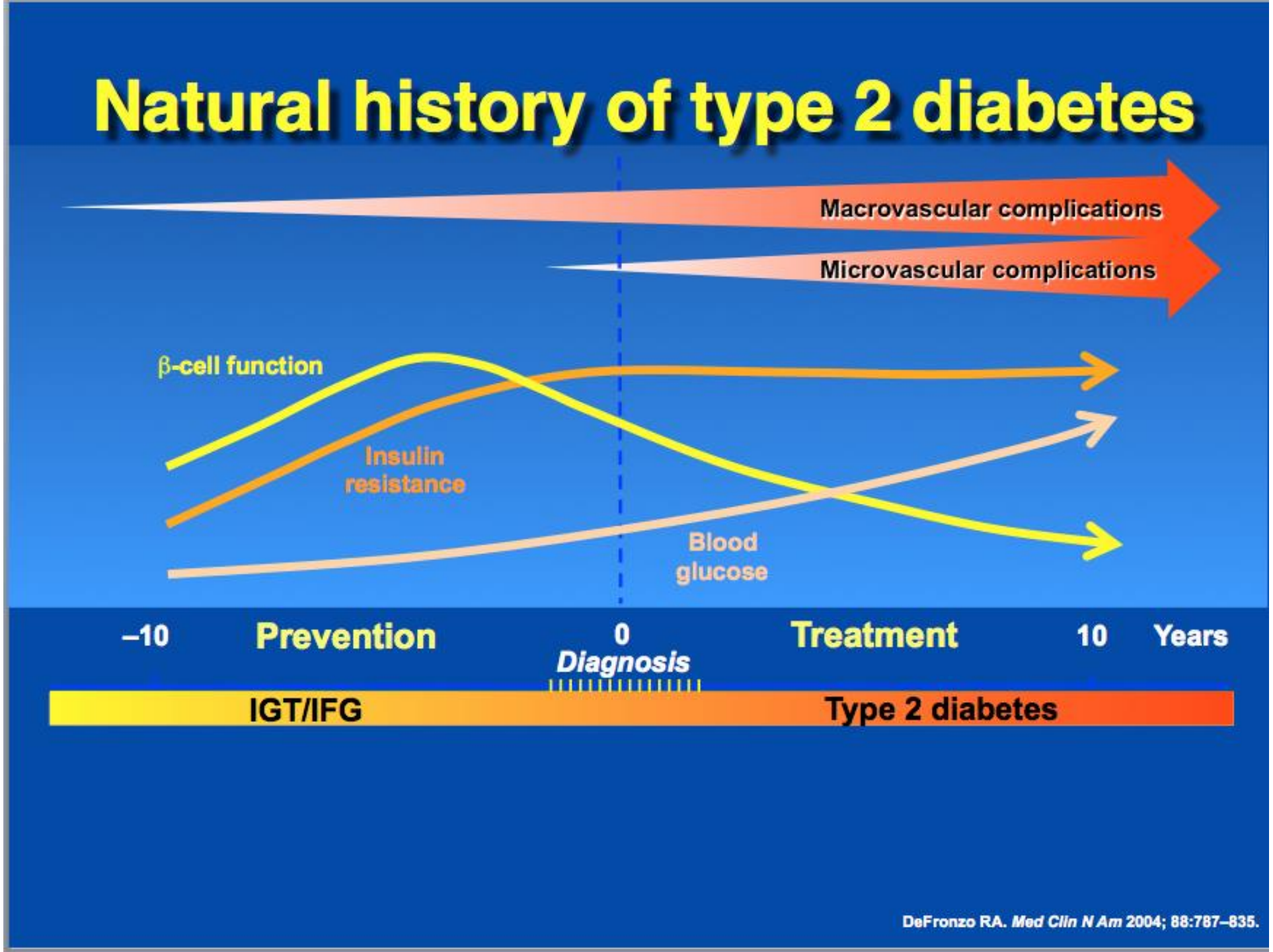
- *Failure to intensify or change therapy*
- *Lack of concern for higher than ideal HbA1c*
- *Complexity of drug regimens*
- *Fear of drug adverse effects*

Poor patient adherence

- *Lack of awareness of complications*
- *Poor diet and lifestyle*
- *Drug adverse effects*
- *Just forgetting to take the drugs*

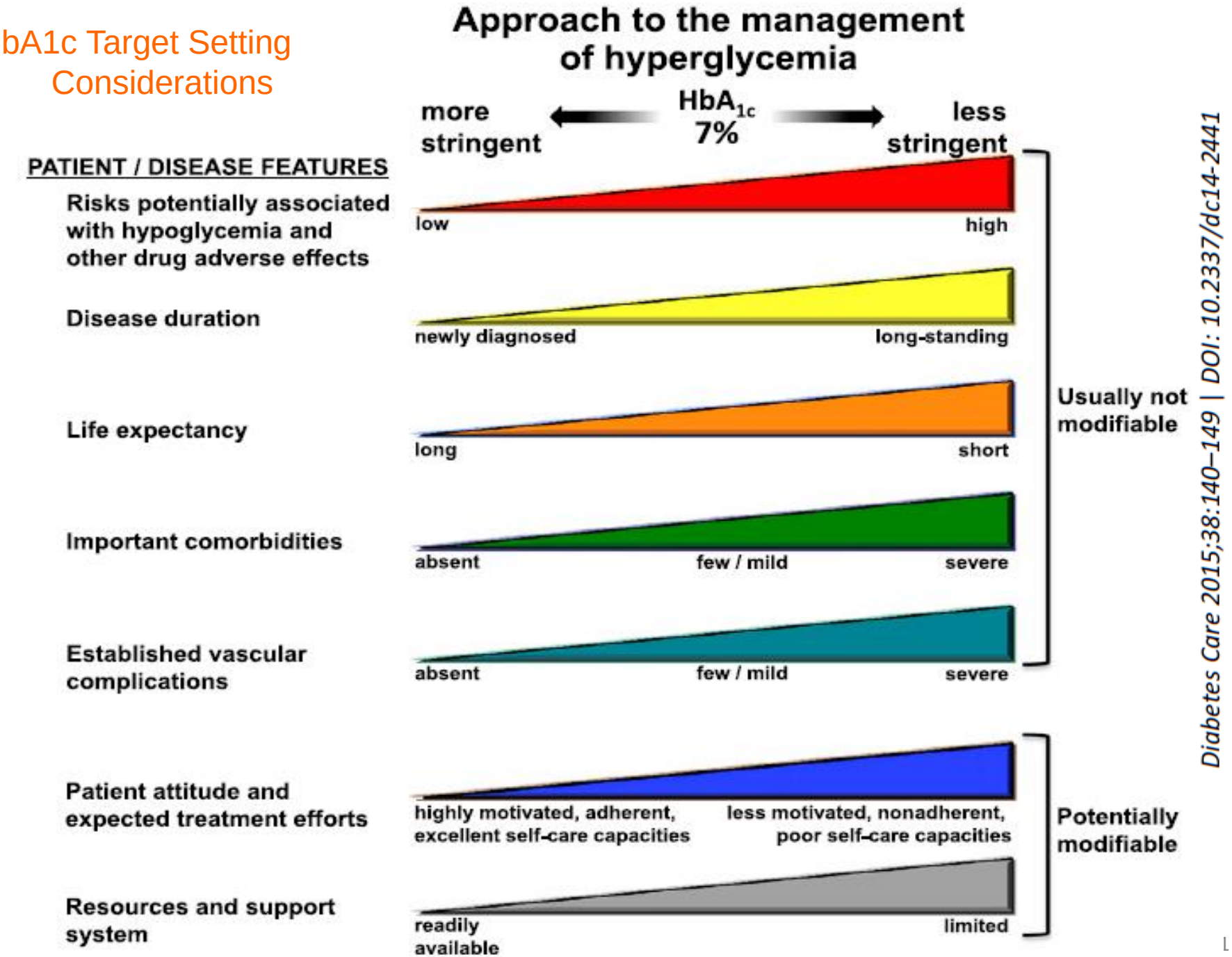
Ref: Del Prato S et al. Diabetes Care 2009;32(Suppl. 2):S217-S222. Grant R et al. Diabetes Care 2007;30:807-812. Miccoli R, Diabetes Care 2011;34 (Suppl.2):S231-S235

Natural history of type 2 diabetes



DeFronzo RA. *Med Clin N Am* 2004; 88:787–835.

HbA1c Target Setting Considerations



Diabetes Care 2015;38:140–149 | DOI: 10.2337/dc14-2441

HbA_{1c} Targets for adults with type 2 diabetes

Individualising glycaemic targets

		HbA1C (%)
General target		≤7.0
Specific clinical situations	**Therapy**	
Diabetes of short duration and no clinical cardiovascular disease	Lifestyle ± metformin	≤6.0
	Any anti-diabetic agents other than metformin or insulin	≤6.5
	Requiring insulin	≤7.0
Pregnancy/planning pregnancy		≤6.0
Diabetes of longer duration or clinical cardiovascular disease	Any	≤7.0
Recurrent severe hypoglycaemia or hypoglycaemia unawareness	Any	≤8.0

Reproduced from ADS Position Statement: Individualisation of HbA1c Targets (Sep 2009)

AUSTRALIAN BLOOD GLUCOSE TREATMENT ALGORITHM
FOR TYPE 2 DIABETES

Australian Diabetes Society

All patients should receive education regarding lifestyle measures: healthy diet, physical activity and weight control
Determine the individual's HbA_{1c} target – this will commonly be ≤ 53 mmol/mol (7.0%).
If not at target, or if an HbA_{1c} reduction of ≥ 0.5% is not achieved after 3 months, move down the algorithm.

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

Metformin | SU | Insulin | Acarbose | DPP-4 inhibitor | SGLT2 inhibitor | TZD

If HbA_{1c} target not achieved in 3 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
- reinforce lifestyle measures

Second line: If metformin was not used first line, add it now, if not contraindicated.
Choice of second line agent to add to metformin should be guided by clinical factors/considerations, contraindications, side effect profile and cost.

DPP-4 inhibitor | SGLT2 inhibitor | SU | GLP-1RA | Insulin* | Acarbose | TZD

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THEN

If on triple oral therapy		If on GLP-1RA		If on basal insulin*
Switch ≥ 1 oral agent to GLP-1RA or insulin* or another oral agent†	OR	Change to basal or premixed/ coformulated insulin*	Add basal or premixed/ coformulated insulin*	OR	Add SGLT2 inhibitor or GLP-1RA or basal bolus or basal plus insulin or change to premixed insulin

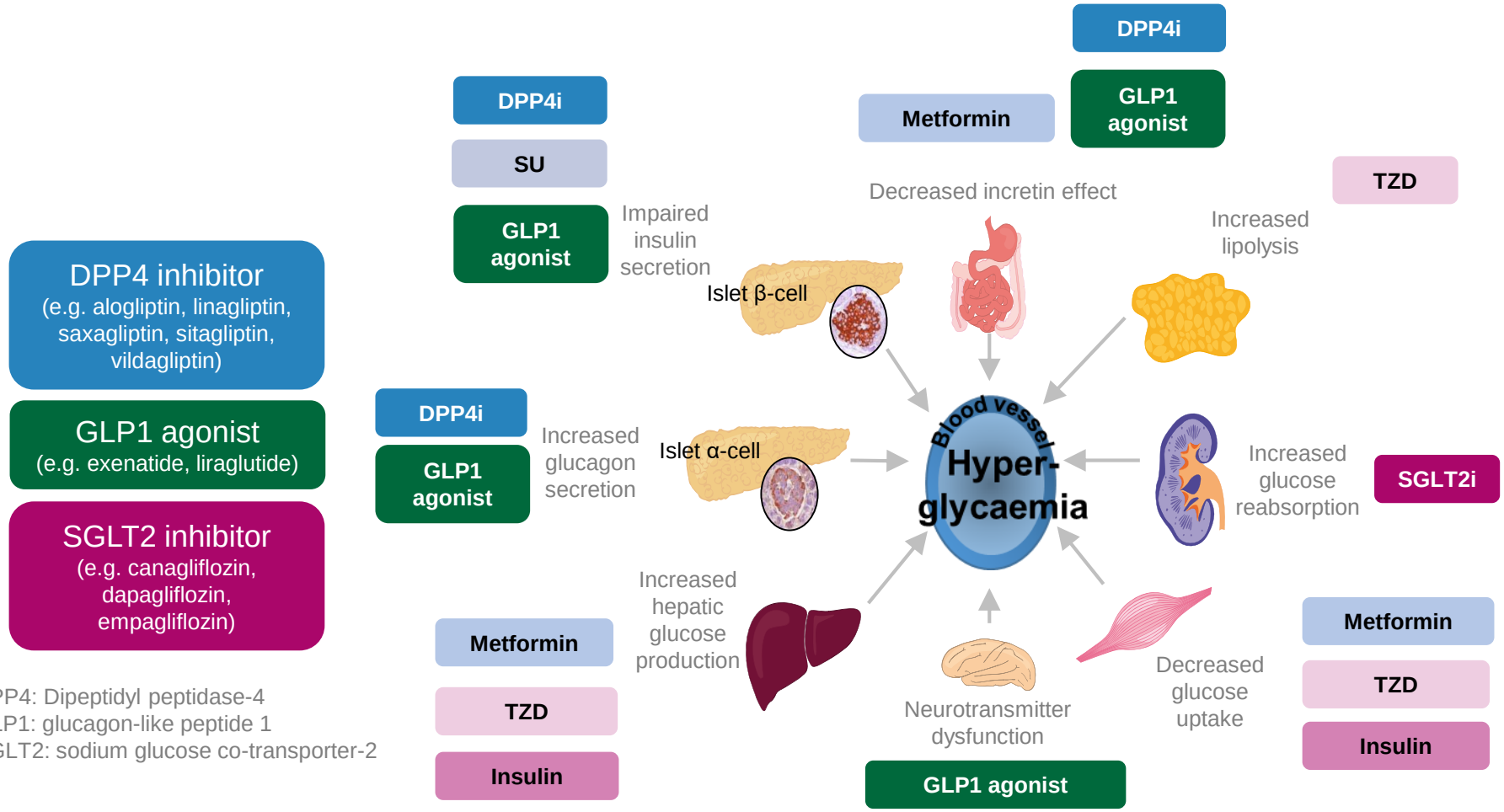
PBS – Pharmaceutical Benefits Scheme, SU–sulfonylurea, TZD– thiazolidinedione, DPP-4 – dipeptidyl peptidase-4, GLP-1RA– glucagon like peptide 1 receptor agonist, SGLT2 – sodium glucose transporter.
Dark blue boxes indicate usual therapeutic strategy (order is not meant to denote any specific preference); usual refers to commonly available, evidence based, cost effective therapy.
White boxes indicate alternate approaches (order is not meant to denote any specific preference).
Red outlines indicate the classes of glucose lowering agent that include PBS subsidised products.
* Unless metformin is contraindicated, or not tolerated, it is often therapeutically useful to continue it in combination with insulin.
† Switching an oral agent is likely to have the smallest impact on glycaemia.

diabetes australia

The National Diabetes Services Scheme is an initiative of the Australian Government administered with the assistance of Diabetes Australia.

ndss national diabetes services scheme

CURRENT GLUCOSE-LOWERING THERAPIES WORK ACROSS MULTIPLE MECHANISMS OF ACTION[1-3]



1. Inzucchi SE *et al. Diabetes Care* 2012; 35: 1364–79. 2. DeFronzo RA. *Diabetes* 2009; 58: 773–95. 3. Bailey CJ. The Role of the Kidney in Glucose Control. Available from: www.medscape.org. Accessed 7 April 2014.

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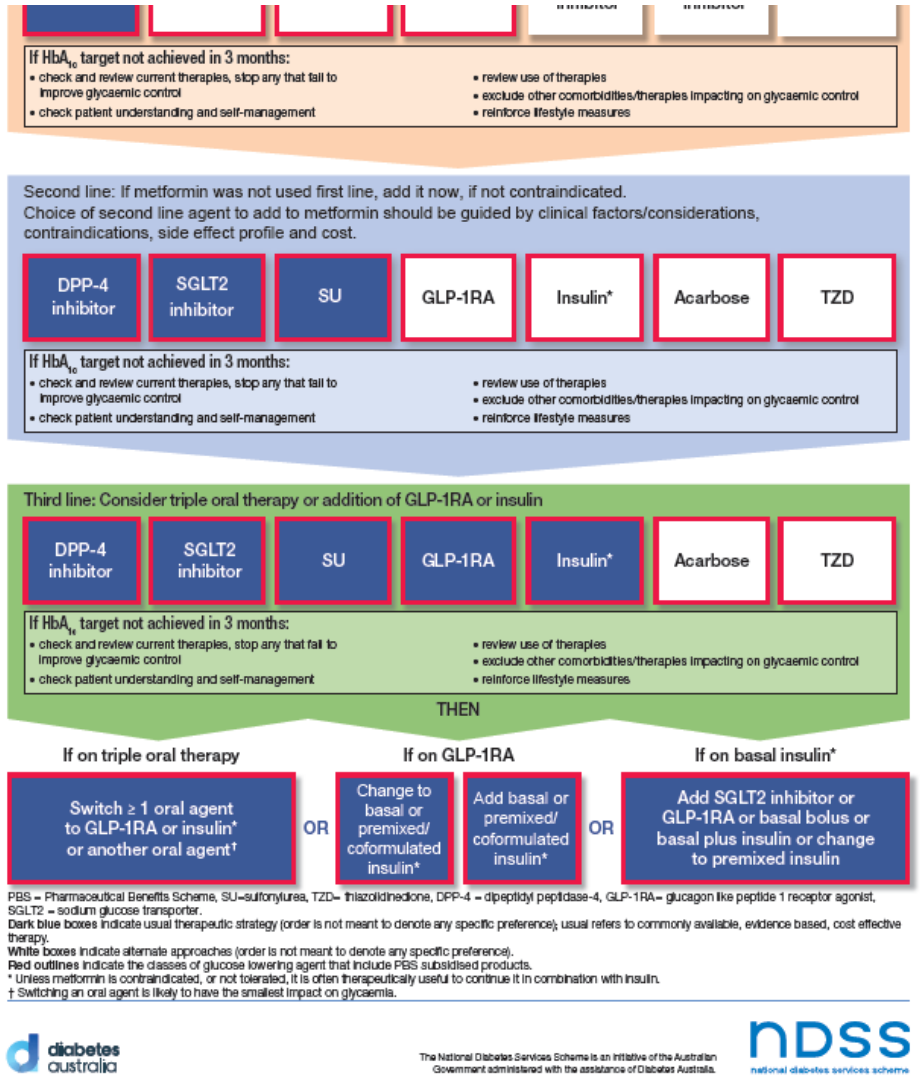

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Lifestyle Modification

- Exercise - 150 min or more of moderate-to-vigorous intensity aerobic activity per week with 2–3 sessions/week of resistance exercise on non-consecutive days
- Diet - There is not a one-size-fits-all eating pattern for individuals with diabetes, and meal planning should be individualized

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Metformin

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Insulin | Acarbose | DPP-4 inhibitor | SGLT2 inhibitor | TZD

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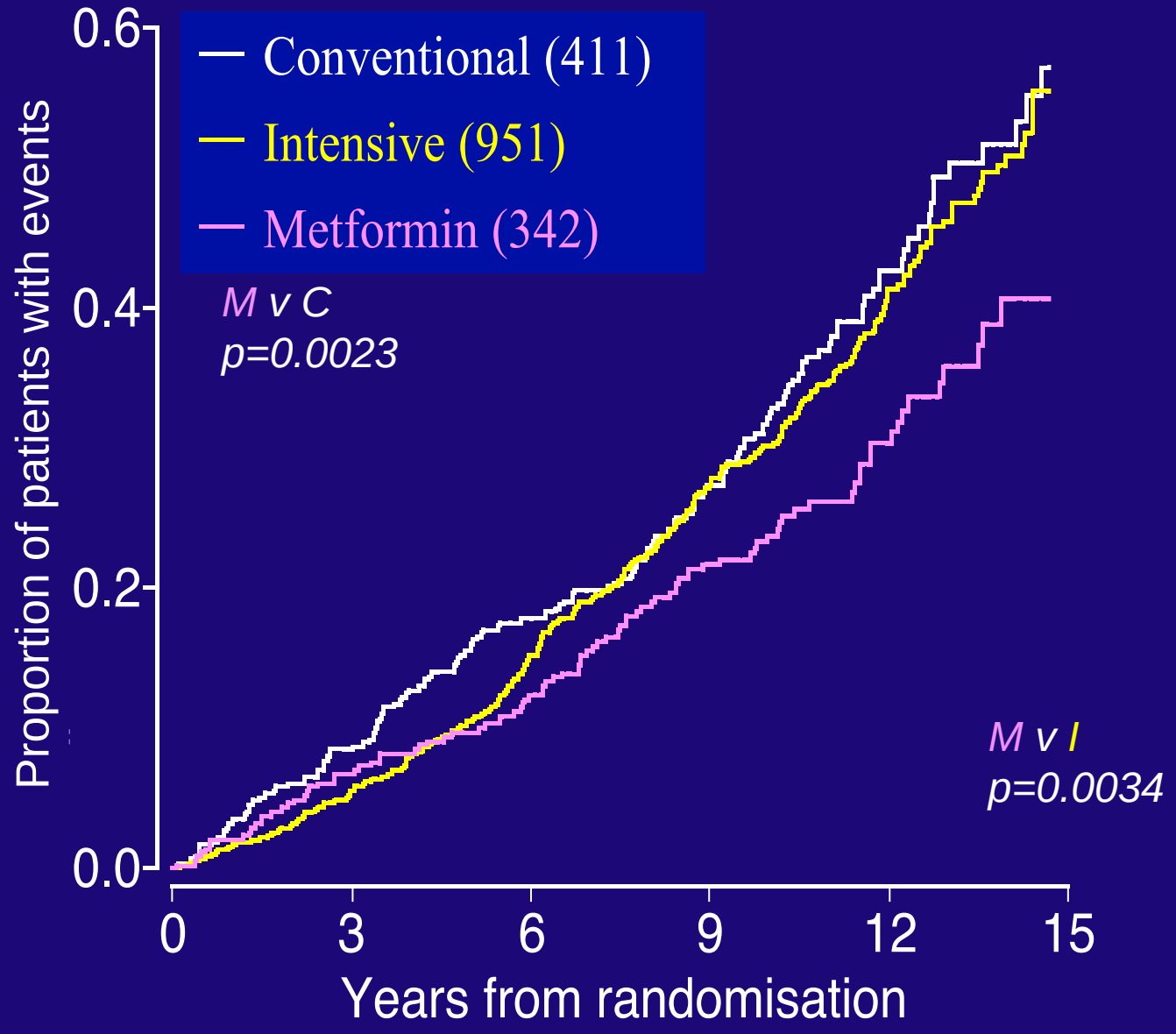
Metformin

- 60 years old but still first line in type 2 diabetes
- Inhibits hepatic glucose production
- Small effect on insulin sensitivity and gut glucose absorption

UKPDS: Effect of metformin vs. insulin/SU

overweight patients



ukpds

Metformin

+ No weight gain / small weight loss

+ Hypoglycaemia rare

+ CV neutral (possible benefit vs. SU)

- GI intolerance: nausea (less with XR), diarrhoea

- C/I in renal failure: GFR 30-40 max 1000mg; GFR <30 stop

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DPP-4 inhibitor

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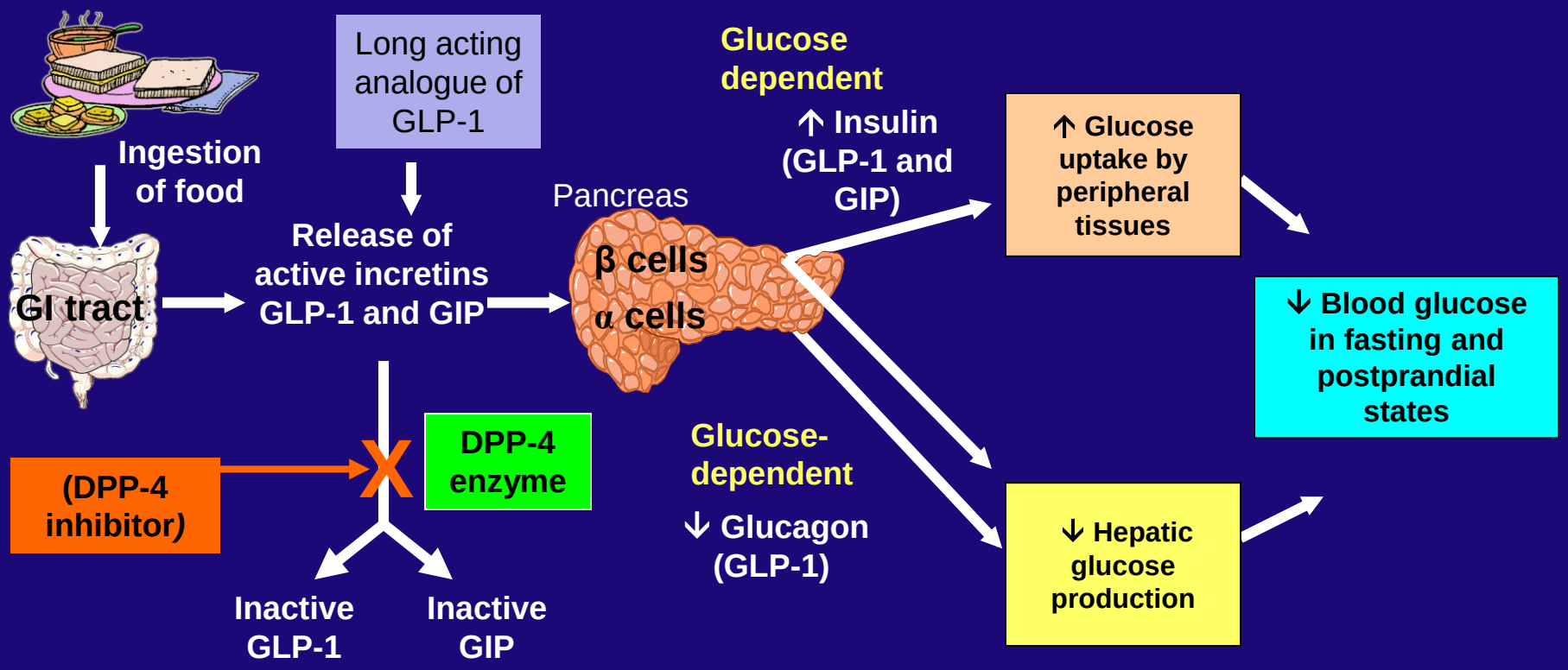
DPP4 inhibitors available in Australia

- alogliptin (Nesina®)
- linagliptin (Trajenta®)
- saxagliptin (Onglyza®)
- sitagliptin (Januvia®)
- vildagliptin (Galvus®)

Mechanism of Action of DPP4i

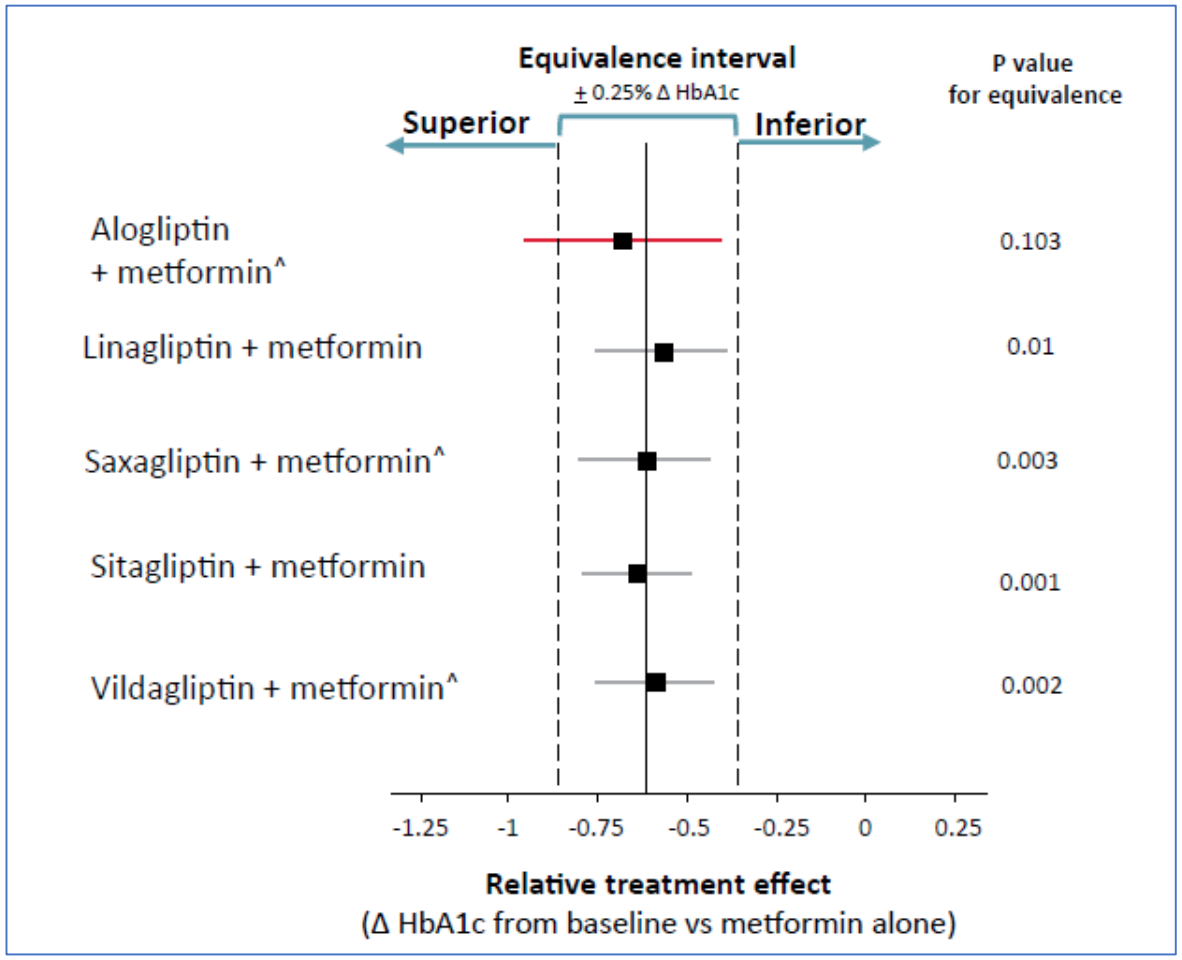


Incretin hormones GLP-1 and GIP are released by the intestine throughout the day, and their levels increase in response to a meal.

Concentrations of the active intact hormones are increased by DPP4i, thereby increasing and prolonging the actions of these hormones.

Therapeutic Equivalence of DPP4 inhibitors

in combination with metformin in patients with T2D[1,2]



Independent analysis of clinical data from a systematic review including 38 RCTs of DPP4 inhibitor/metformin combination therapy vs metformin alone.[2]

^ Heterogeneity may be present.

1. A. Messori et al. Diabetes Ther (2014) 5:341-344. 2. P. Craddy et al. Diabetes Ther (2014) 5:1-41

DPP4 inhibitors (“gliptins”)

+ No weight gain

+ Very well tolerated (SE’s very rare)

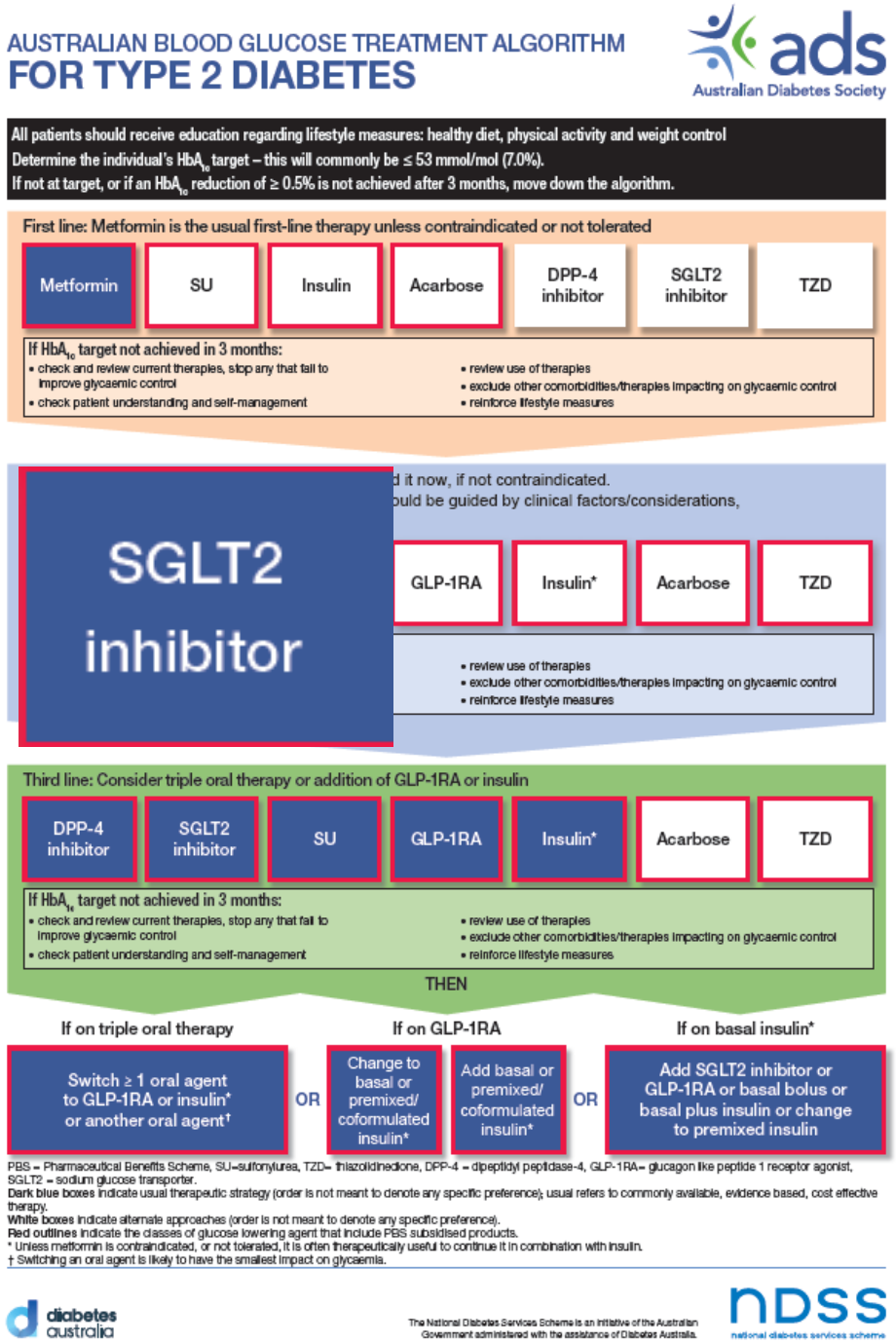
+ CV neutral (possible slight increase in HF with saxagliptin)

- Renal excretion – need to reduce dose except for linagliptin

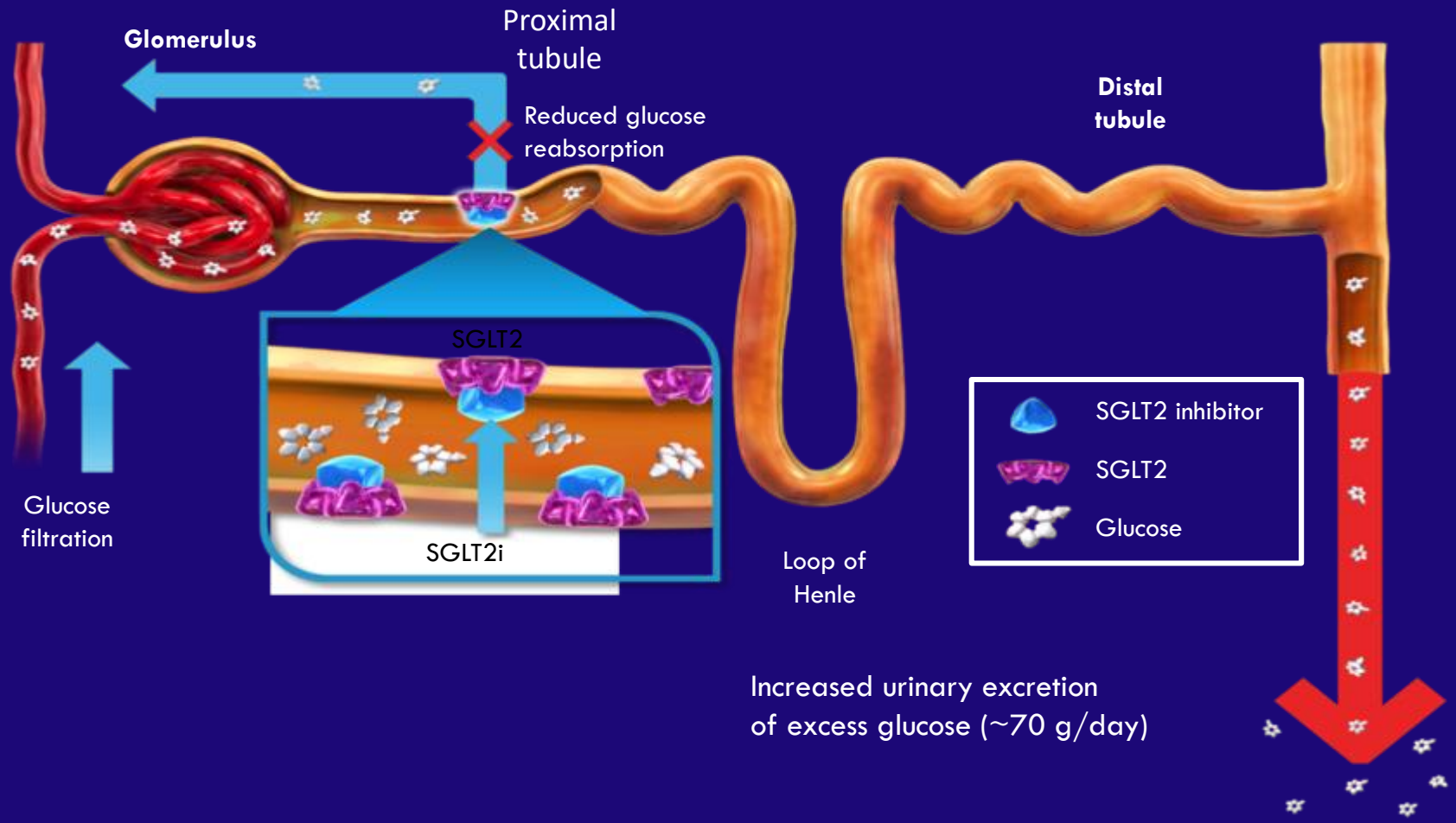
dapagliflozin

empagliflozin

ertugliflozin

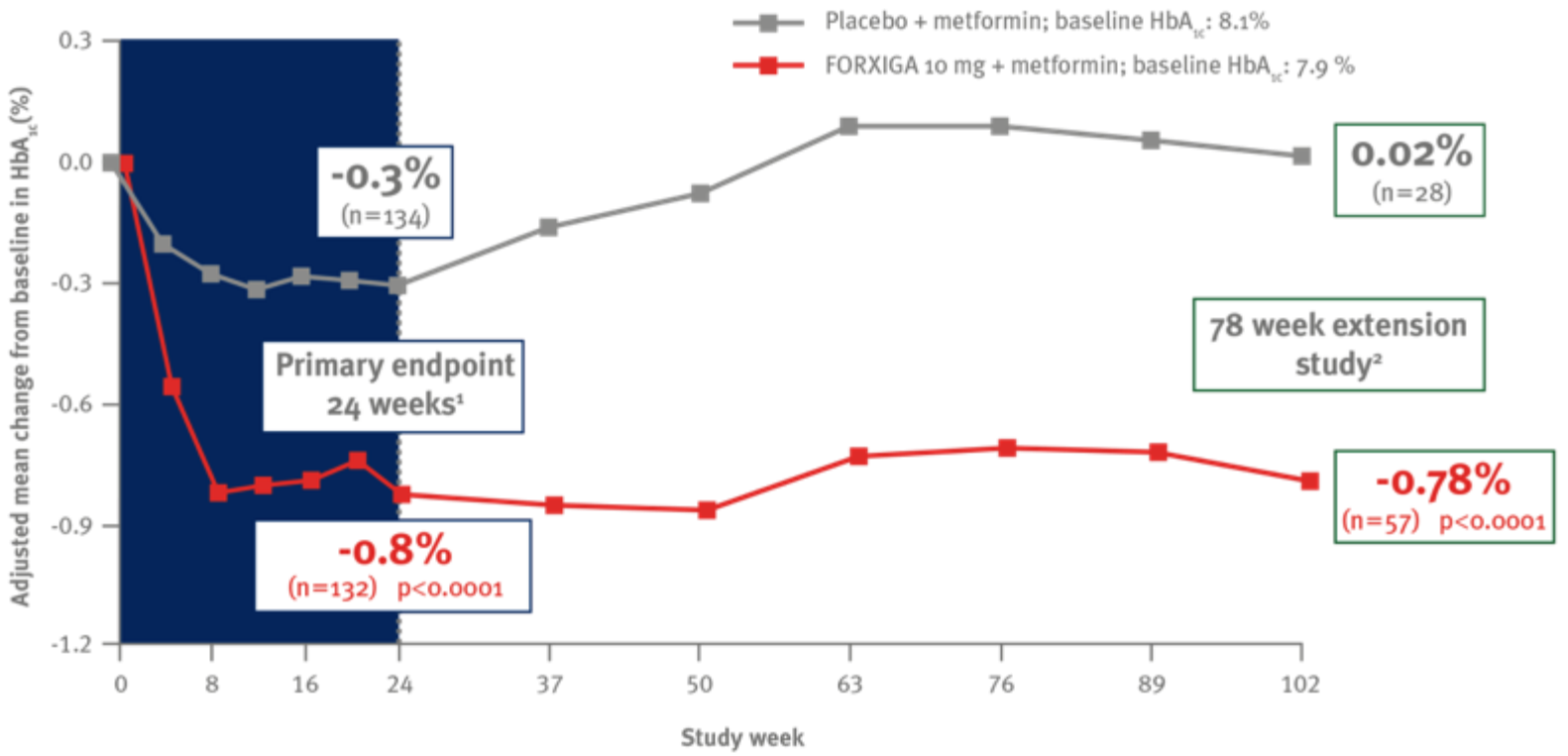


SGLT2 inhibitors: mechanism of action



Gerich JE, Bastien A. Expert Rev Clin Pharmacol 2011;4:669–683.

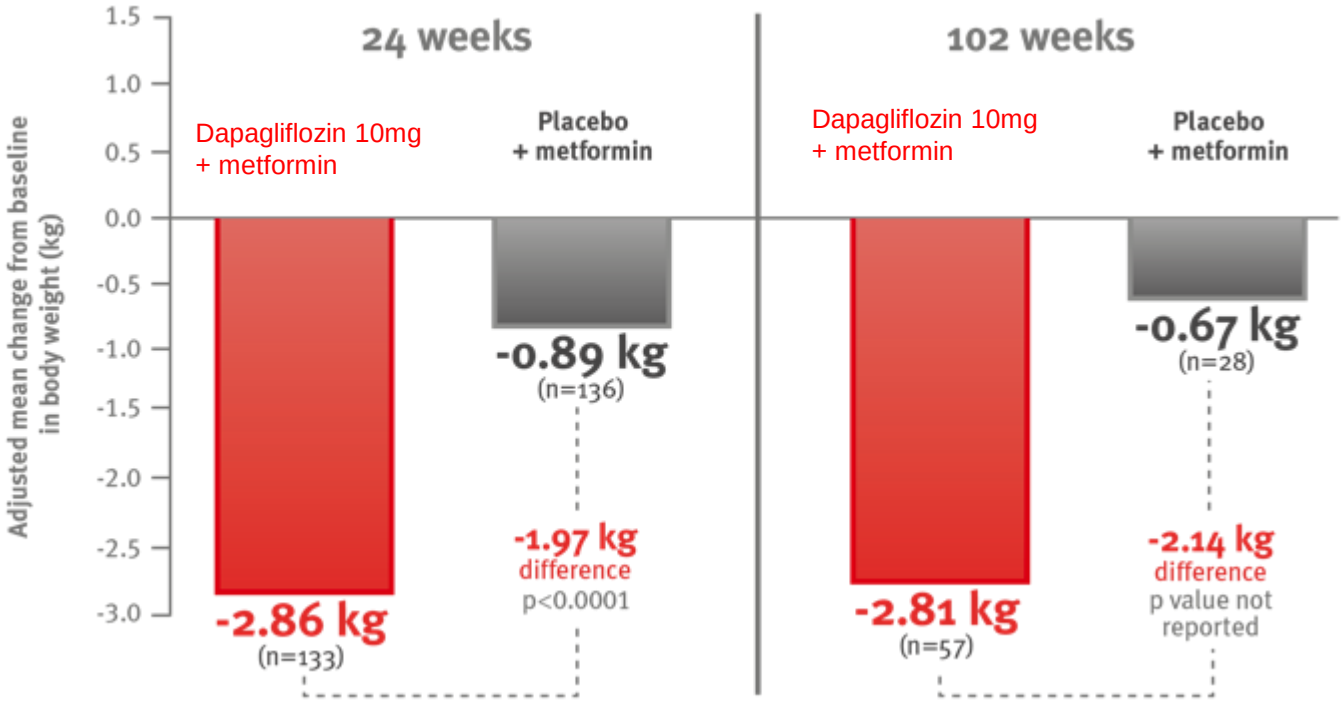
Sustained HbA_{1c} reductions[1,2] with dapagliflozin+metformin vs metformin



Adapted from Bailey CJ, et al.[1,2]

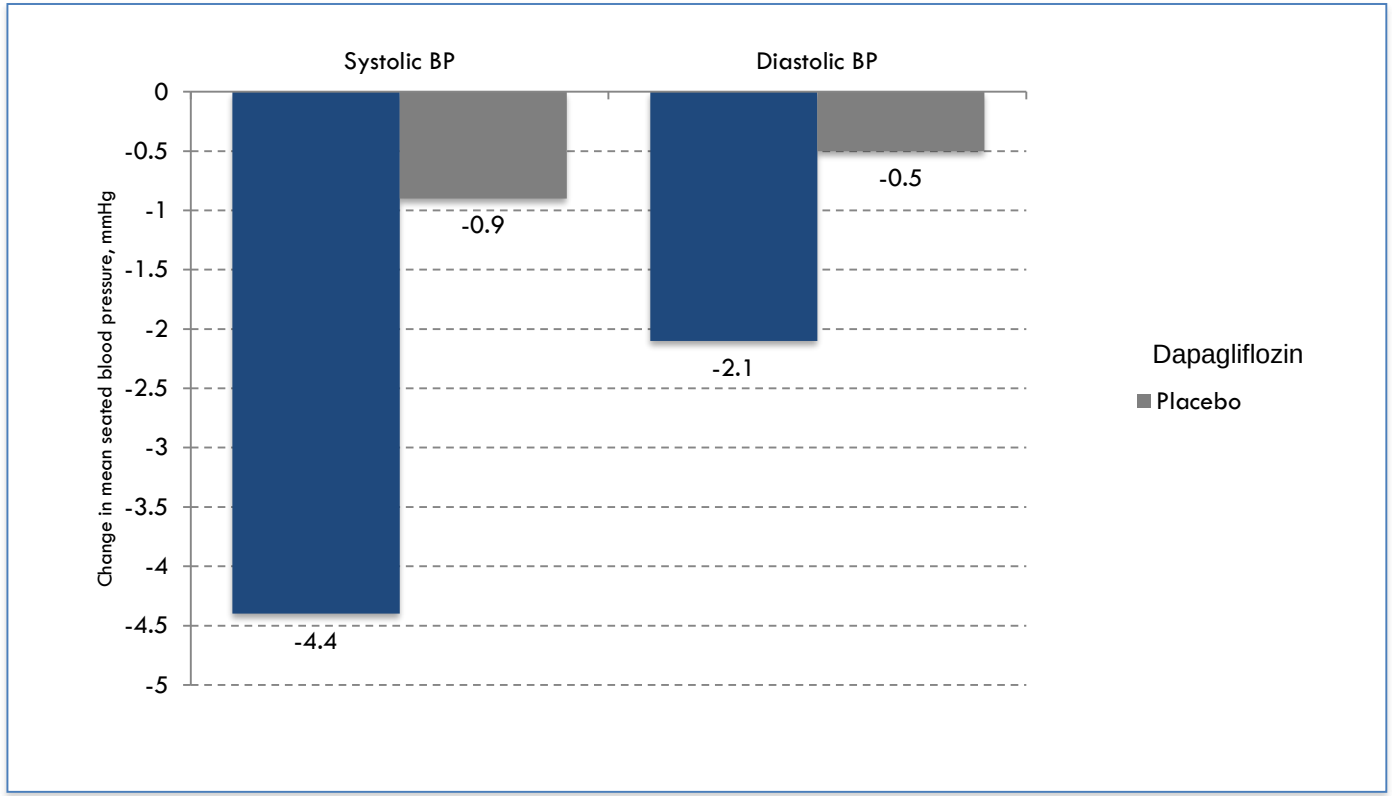
1. Bailey CJ, et al. Lancet 2010;375:2223–2233.
2. Bailey CJ, et al. BMC Medicine 2013;11:43:1-10.

SGLT2 inhibitor added to metformin: effect on weight



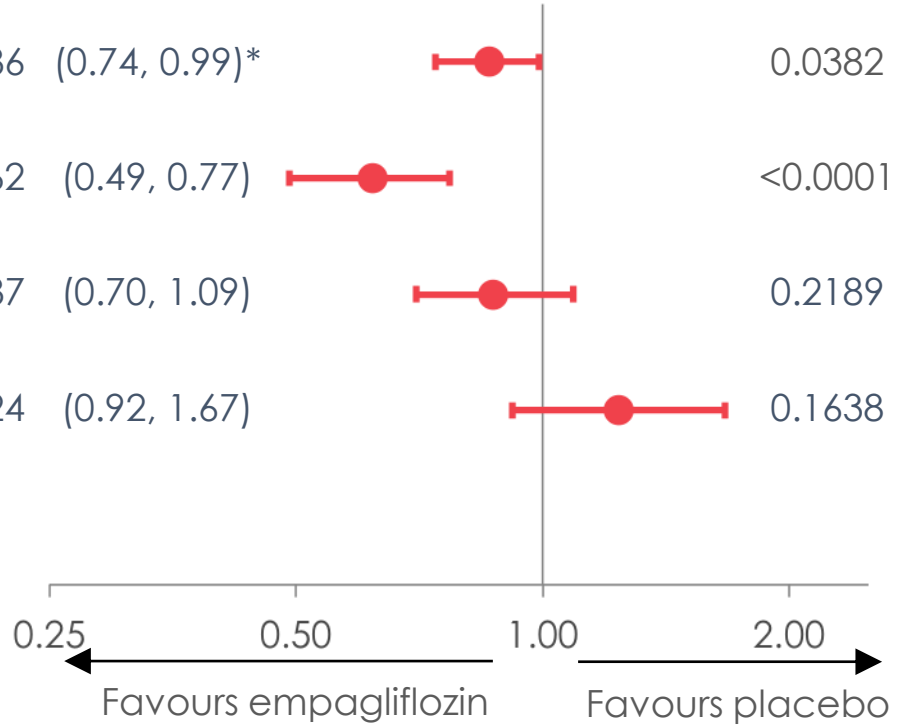
Bailey CJ, et al. Lancet 2010;375:2223–2233.

SGLT2 inhibitor added to metformin: effect on blood pressure



CV death, MI and stroke

	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	p-value
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638



Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction
*95.02% CI

SGLT2 inhibitors

+ Weight loss 2-3 kg
+ Hypoglycaemia rare
+ CV benefit in patients with existing CVD

- Genital infections
- Polyuria
- Poor efficacy at low GFR (No efficacy at GFR<45)

AUSTRALIAN BLOOD GLUCOSE TREATMENT ALGORITHM
FOR TYPE 2 DIABETES

Australian Diabetes Society

All patients should receive education regarding lifestyle measures: healthy diet, physical activity and weight control
Determine the individual's HbA_{1c} target – this will commonly be ≤ 53 mmol/mol (7.0%).
If not at target, or if an HbA_{1c} reduction of ≥ 0.5% is not achieved after 3 months, move down the algorithm.

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

Metformin | SU | Insulin | Acarbose | DPP-4 inhibitor | SGLT2 inhibitor | TZD

If HbA_{1c} target not achieved in 3 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
- reinforce lifestyle measures

Second line: If n… traindicated.
Choice of secon… clinical factors/considerations, contraindication…

DPP-4 inhibitor | **SU** | Insulin* | Acarbose | TZD

If HbA_{1c} target not…
- check and review c… e of therapies
- Improve glycaemic … other comorbidities/therapies impacting on glycaemic control
- check patient unde… lifestyle measures

Third line: Consider triple oral therapy or addition of GLP-1RA or insulin

DPP-4 inhibitor | SGLT2 inhibitor | SU | GLP-1RA | Insulin* | Acarbose | TZD

If HbA_{1c} target not achieved in 3 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
- reinforce lifestyle measures

THEN

If on triple oral therapy		If on GLP-1RA		If on basal insulin*
Switch ≥ 1 oral agent to GLP-1RA or insulin* or another oral agent†	OR	Change to basal or premixed/ coformulated insulin*	Add basal or premixed/ coformulated insulin*	OR	Add SGLT2 inhibitor or GLP-1RA or basal bolus or basal plus insulin or change to premixed insulin

PBS – Pharmaceutical Benefits Scheme, SU–sulfonylurea, TZD– thiazolidinedione, DPP-4 – dipeptidyl peptidase-4, GLP-1RA– glucagon like peptide 1 receptor agonist, SGLT2 – sodium glucose transporter.
Dark blue boxes indicate usual therapeutic strategy (order is not meant to denote any specific preference); usual refers to commonly available, evidence based, cost effective therapy.
White boxes indicate alternate approaches (order is not meant to denote any specific preference).
Red outlines indicate the classes of glucose lowering agent that include PBS subsidised products.
* Unless metformin is contraindicated, or not tolerated, it is often therapeutically useful to continue it in combination with insulin.
† Switching an oral agent is likely to have the smallest impact on glycaemia.

diabetes australia

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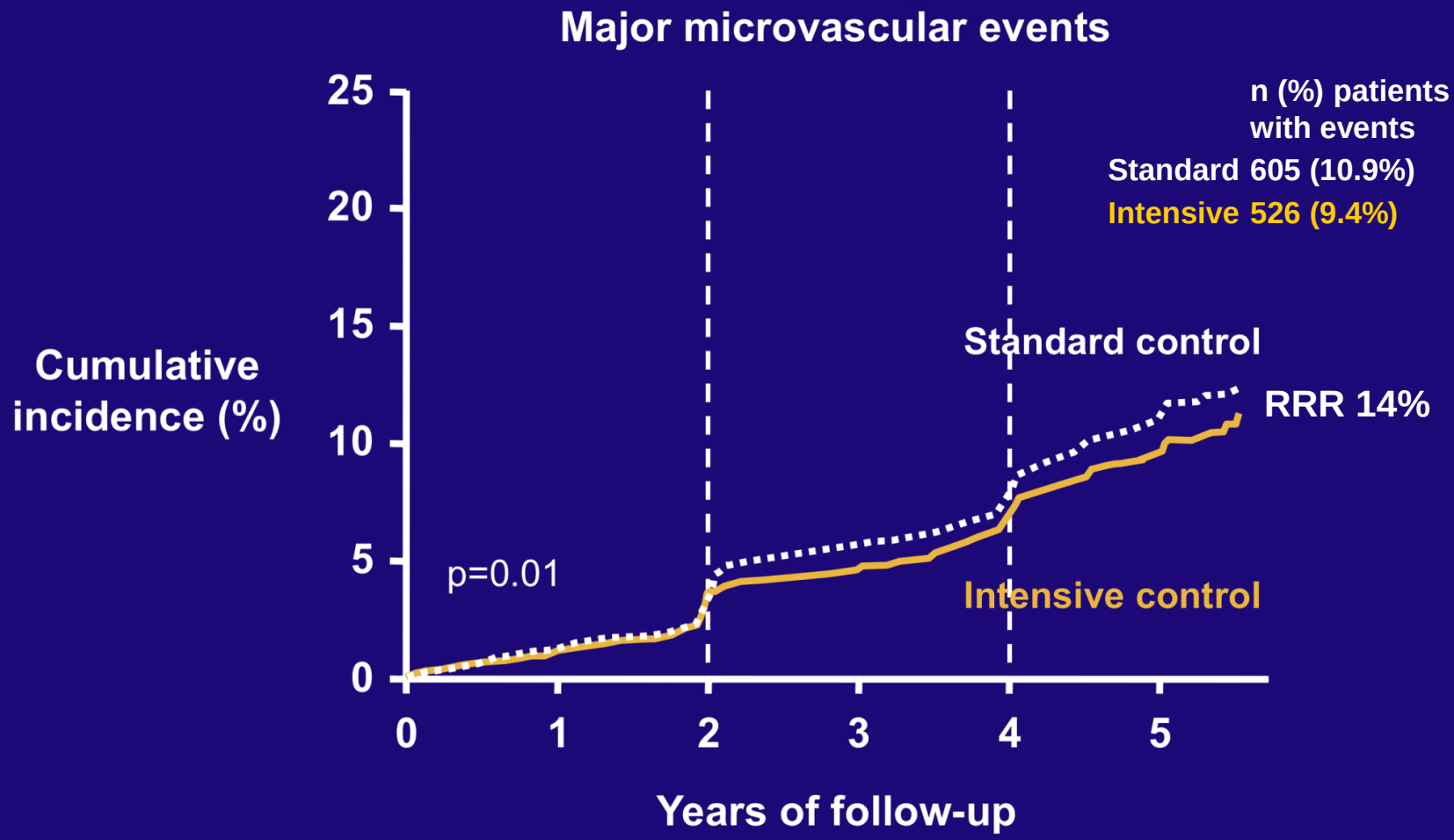
ndss national diabetes services scheme

Sulphonylureas

Stimulate unregulated insulin secretion from the beta-cell

- Gliclazide
- Glibenclamide
- Glimeperide
- Glipizide

Effect of intensive glucose control with SU (gliclazide) on major microvascular complications



No. at risk

Intensive therapy	5571	5495	5430	5358	5233	5120	5055	4968	4824	4258	1992	473
Standard therapy	5569	5498	5431	5353	5207	5069	4995	4911	4764	4204	2024	494

Major microvascular events were defined as new or worsening nephropathy or retinopathy
Additional data on microvascular events were collected at the 1-year and 2-year study visits
RRR: relative risk reduction

ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560–2572.

Sulphonylureas

+ Shown to reduce diabetes endpoints in clinical trials

+ Well tolerated (SE's rare apart from hypoglycaemia)

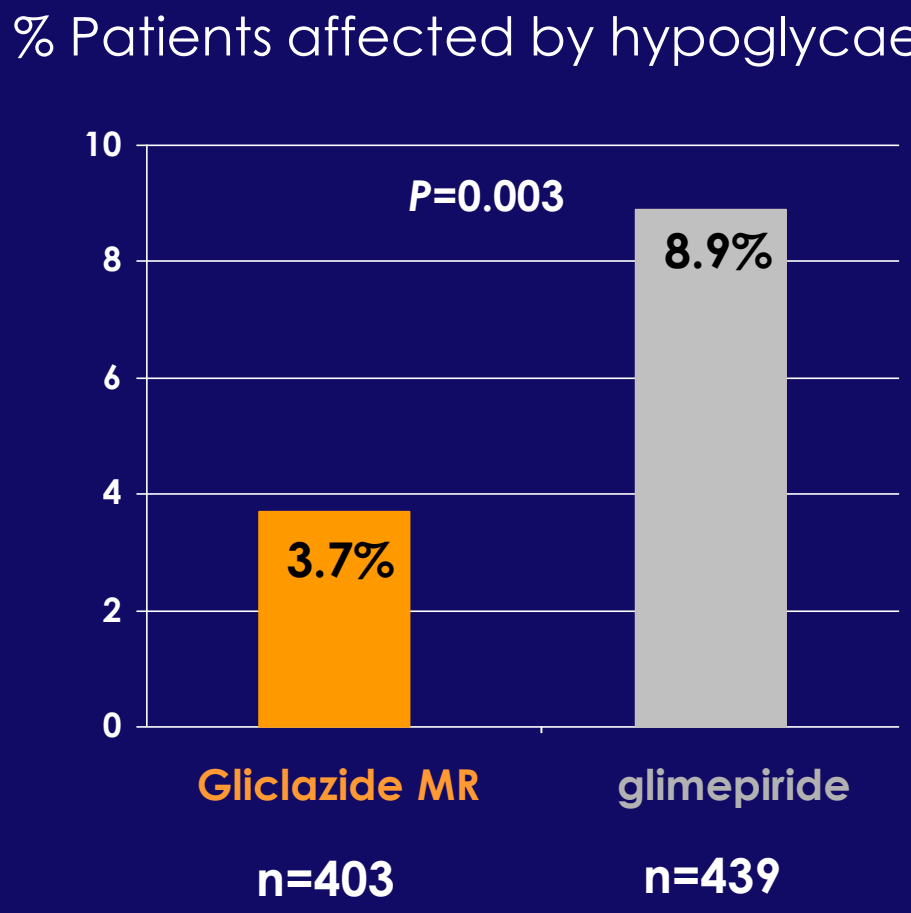
- Risk of hypoglycaemia (gliclazide less than other SU)

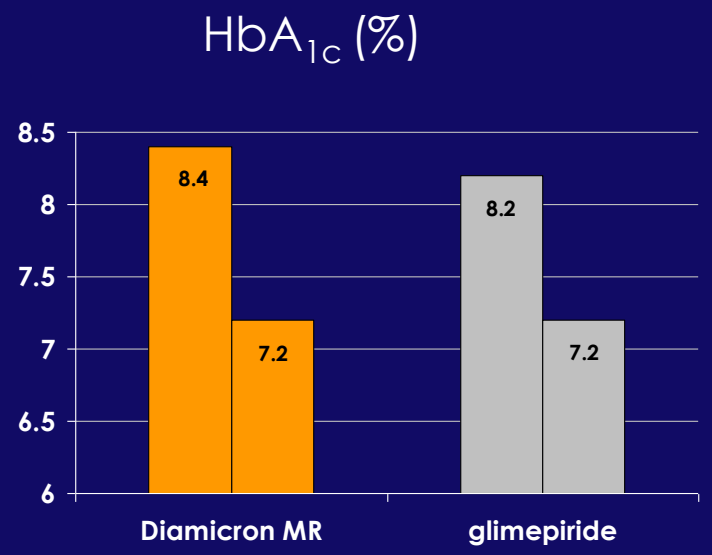
- Weight gain – 1-2 kg reported

- Possible adverse CV effect vs. metformin (<u>not</u> gliclazide)

Effect of gliclazide vs. glimeperide on hypoglycaemia

(Symptoms with blood glucose < 3.0 mmol/L)





G. Schernthaner, U. Di Mario, A. Grimaldi. *Diabetologia*.2003;46:A281

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- reinforce lifestyle measures

Second line: If metformin was not us… Choice of second line agent to add t… derations, contraindications, side effect profile a…

DPP-4 inhibitor | SGLT2 inhibitor | … | …carbose | TZD

GLP-1RA

If HbA_{1c} target not achieved in 3 months:
- check and review current therapies, stop any th… improve glycaemic control
- check patient understanding and self-manage…

…impacting on glycaemic control

Third line: Consider triple oral therapy or addition of GLP-1RA or insulin

DPP-4 inhibitor | SGLT2 inhibitor | SU | GLP-1RA | Insulin* | Acarbose | TZD

If HbA_{1c} target not achieved in 3 months:
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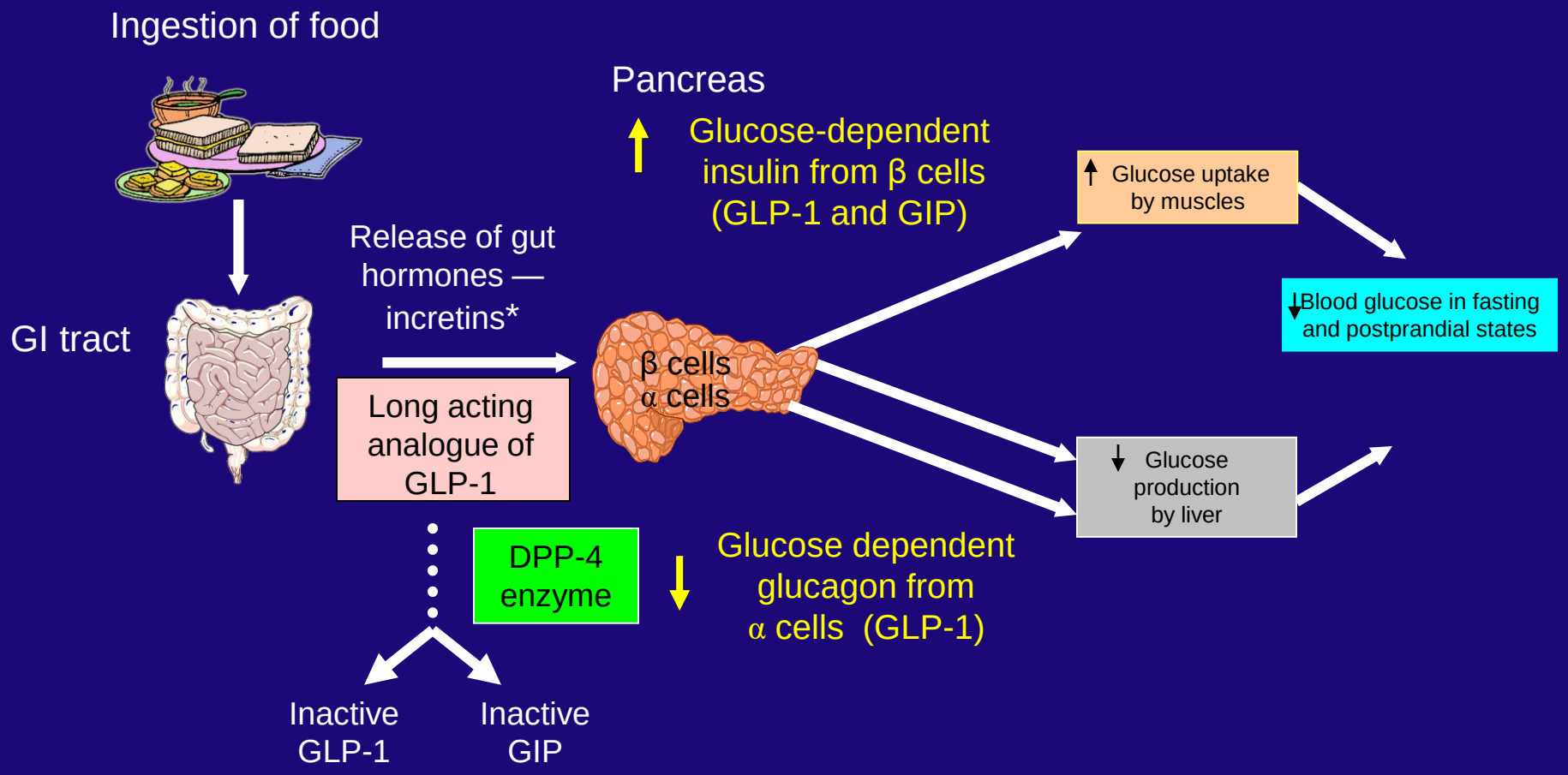
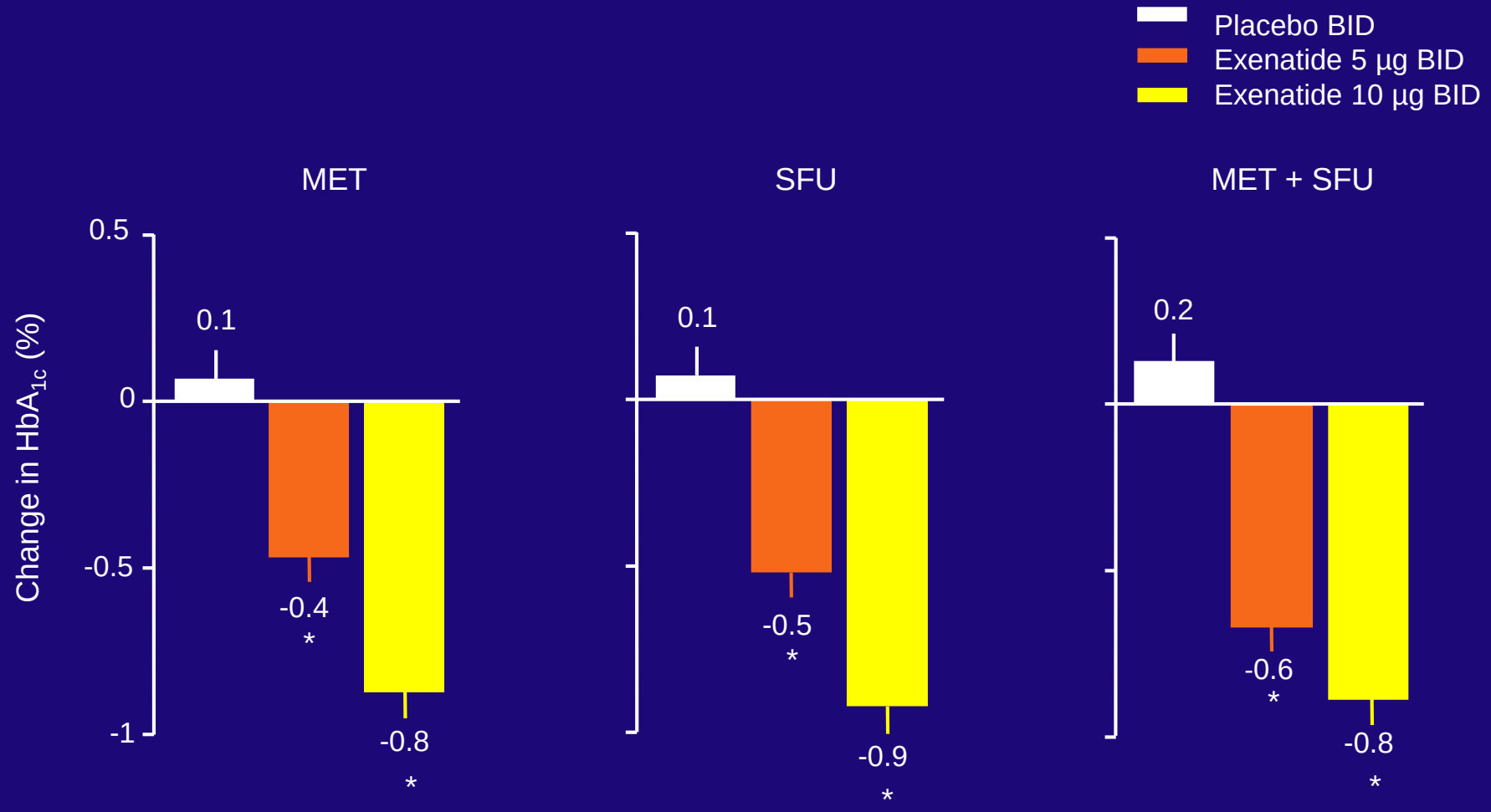
Role of Incretins in Glucose Homeostasis



*Incretins are also released throughout the day at basal levels.

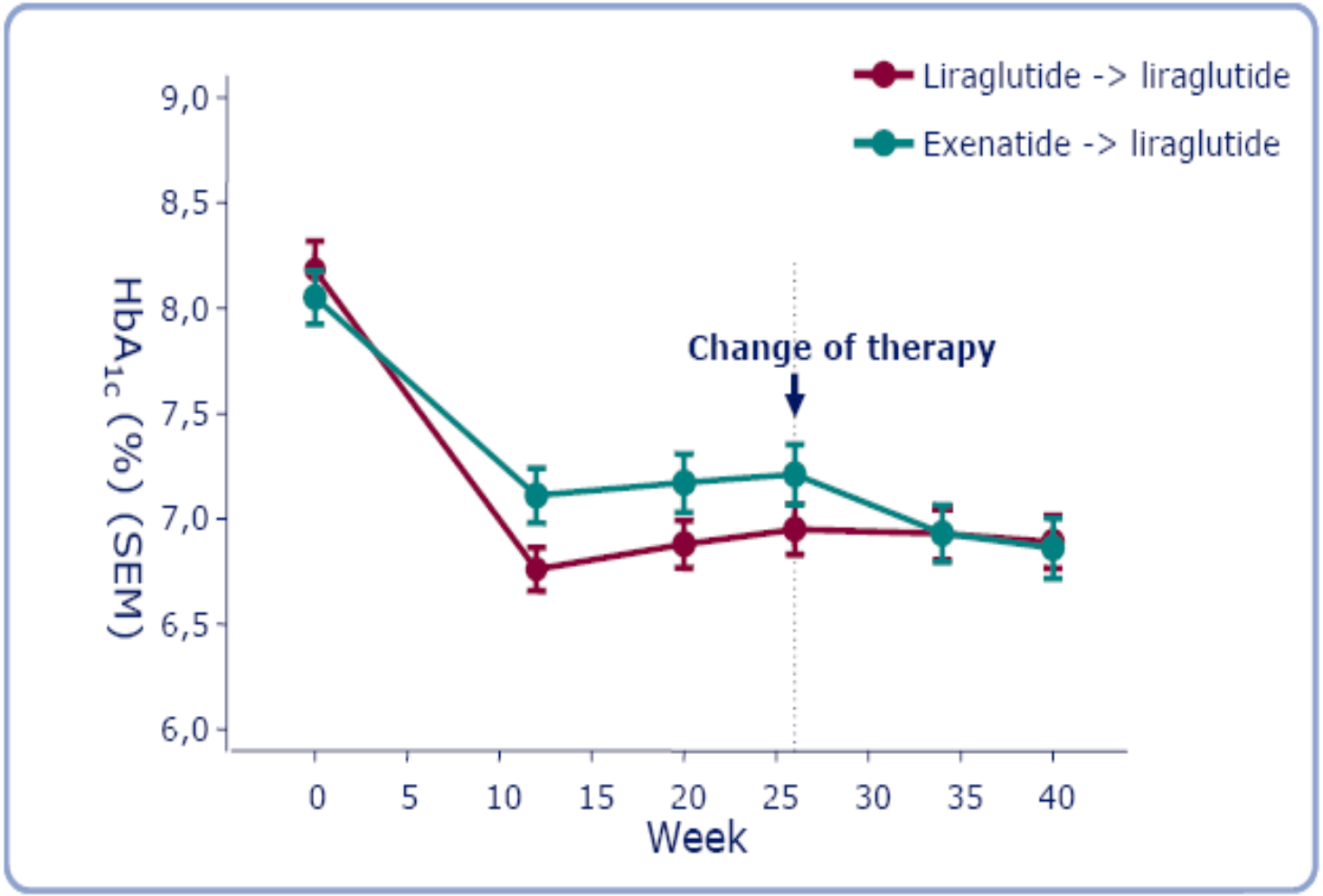
Adapted from Kieffer TJ, Habener JF. *Endocr Rev*. 1999;20:876–913; Ahrén B. *Curr Diab Rep*. 2003;2:365–372; Drucker DJ. *Diabetes Care*. 2003;26:2929–2940; Holst JJ. *Diabetes Metab Res Rev*. 2002;18:430–441.

Effect of exenatide added to metformin or SU on HbA_{1c} at 30 Weeks



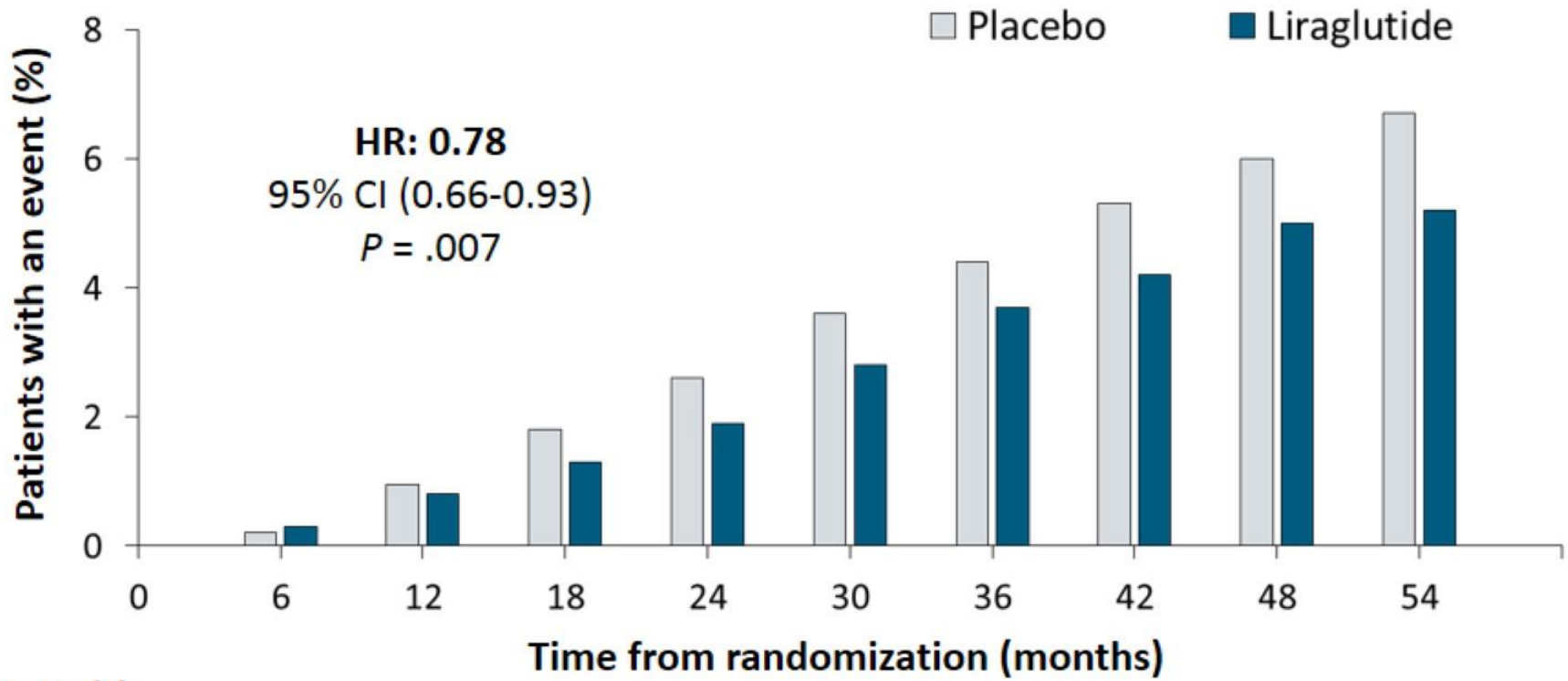
ITT population; Mean (SE); MET (N = 336), SFU (N = 377), MET + SFU (N = 733); *p<.005 vs placebo.
Mean baseline HbA1c ranged from 8.2% to 8.7% across all trial arms.
DeFronzo RA, et al. *Diabetes Care.* 2005;28:1092-1100.; Buse JB, et al. *Diabetes Care.* 2004;27:2628-2635.; Kendall DM, et al. *Diabetes Care.* 2005;28:1083-1091.

LEAD 6 study: Shifting Patients from Exenatide to Liraglutide Improves HbA1c Control



Buse JB et al. *Diabetes Care*. 2010 Mar 23.

LEADER: CV Death



Patients at risk

Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

Marso SP, et al. *N Engl J Med*. 2016;375:311-322.

GLP1 receptor analogues

- exenatide (Byetta, Bydureon)
- dulaglutide (Trulicity)
- liraglutide (Victoza) – not on PBS

\+ Good efficacy

\+ Low hypoglycaemia risk

\+ Weight loss

\+ CV benefit (liraglutide)

\- Nausea common esp. in early days of treatment

\- Administered by s/c injection

Clinical Considerations when choosing oral diabetes medications:

Usual Therapeutic Strategies (second line)

Clinical outcome	DPP-4i	SU	SGLT2i	GLP1 -RA
Risk of Hypoglycaemia	**Lower vs SU**	**Increased risk** (gliclazide less than other SU)	**Lower vs SU**	**Lower vs SU**
Effect on weight	**Neutral** (when added to met vs met +SU)	**Neutral** (gliclazide)/ **Modest gain** (other SUs)	**Modest weight loss**	**Weight loss**
Patients with renal dysfunction	**Reduce dose Except linagliptin (no dose reduction)**	**Increased hypoglycemia risk**	**Efficacy decreases** Contraindicated in moderate renal impairment	**Do not use if GFR <30**

Adapted from RACGP/ Diabetes Australia General practice management of type 2 diabetes 2016-2018

Conclusions

• Good control prevents micro- and macro - vascular complications: early control leads to benefits years later.

• Determine the HbA1C target for each patient based on individual characteristics

• Follow the algorithm: if target HbA1C not reached after 3 months, move down the algorithm.

• Consider co-morbidities and treatment priorities to help you choose the next agent to use.

• Reinforce diet and exercise advice at every step.