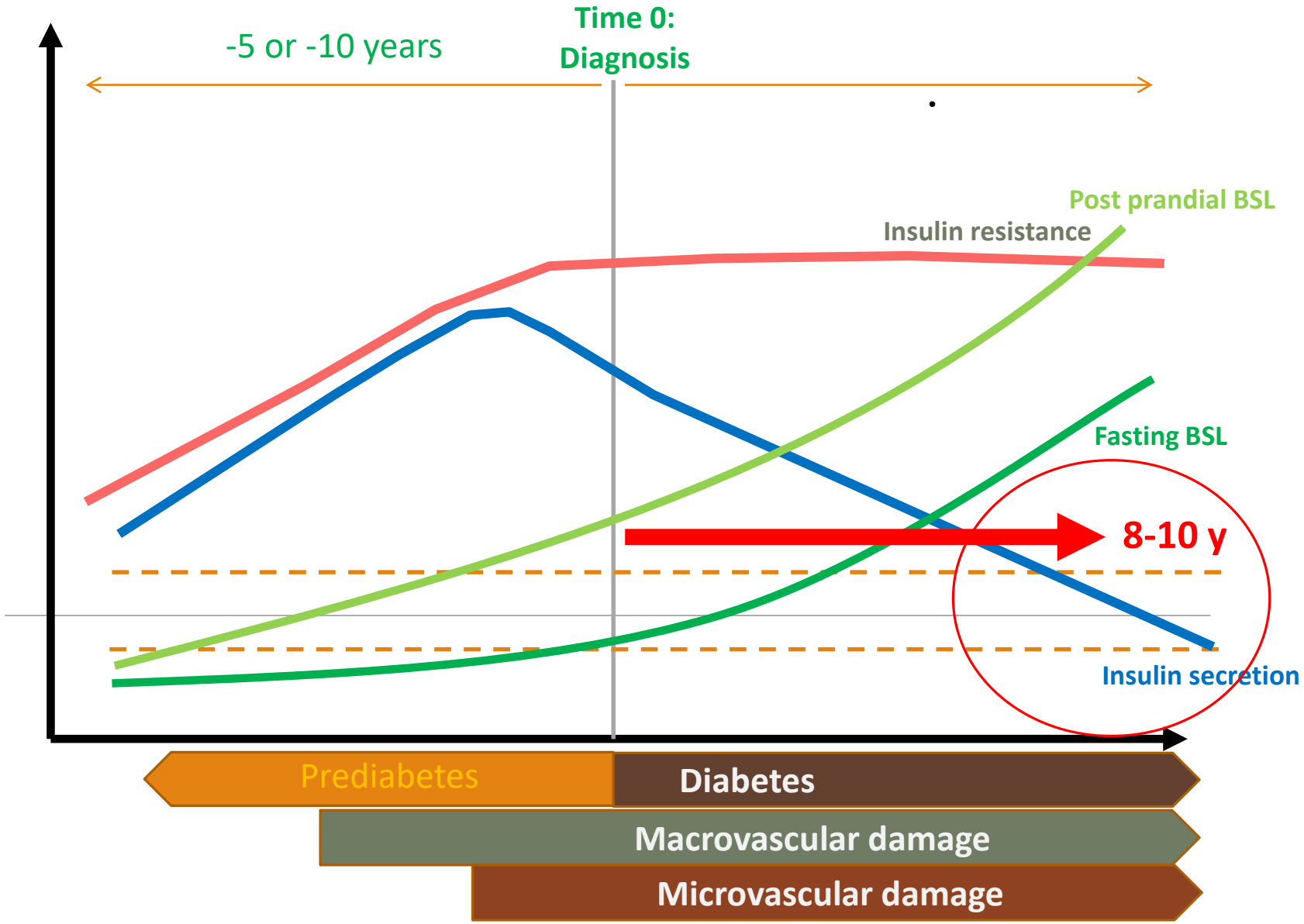
When oral therapy fails

CASE 1 - ANTHONY

The progression of T2D



Anthony

63 year old retired mechanic,

Caucasian

Ex-smoker, nil since 2000

Whiplash injury in motor vehicle accident now with chronic neck pain

Type 2 diabetes diagnosed in 2010 – progressed slowly over the years from pre-diabetes

Gradual increase in body weight from overweight to now obese

Current co-morbidities

METABOLIC

- Obesity
- Sleep apnoea
- Hypertension
- Fatty liver
- Dyslipidaemia
- Tremor –Parkinsons disease?

MECHANICAL

- Cervical spondylosis
- Migraines
- Patello-femoral arthritis
- Achilles tendon calcification
- Plantar fasciitis bilateral
- Benign prostatic hyperplasia

Current Meds

Aldactone 25mg Tablet	1 Tablet In the morning
Atenolol 50mg Tablet	1/2 Daily
Crestor 40mg Tablet	1 Tablet Before bed
Duodart 500mcg; 400mcg Capsule	1 Capsule Daily
Endone 5mg Tablet	1 Tablet In the morning
Imigran 20mg/0.1mL Nasal Spray	1 Spray p.r.n.
Imigran 50mg Tablet	1 Tablet p.r.n.
QTERN (dapagliflozin/saxagliptin) 10mg/5mg	1 tablet In the morning
Metformin XR 1,000mg Tablet	1 Tablet Twice a day
Mobic 7.5mg Tablet	1 Tablet Twice a day
Movicol 13.125g per sachet Sachet	1 Sachet In the evening
MS Contin 10mg Slow Release Tablets	1 Tablet Twice a day
Panadeine Forte 500mg;30mg Tablet	2 Tablets Three times a day p.r.n.
Somac 40mg Tablet	1 Tablet Before bed
Telmisartan /Amlodipine 80mg; 5mg Tablet	1 Tablet In the morning
Topamax 50mg Tablet	1 Tablet Twice a day

Current Findings

BP 131/69 mmHg

BMI – see later

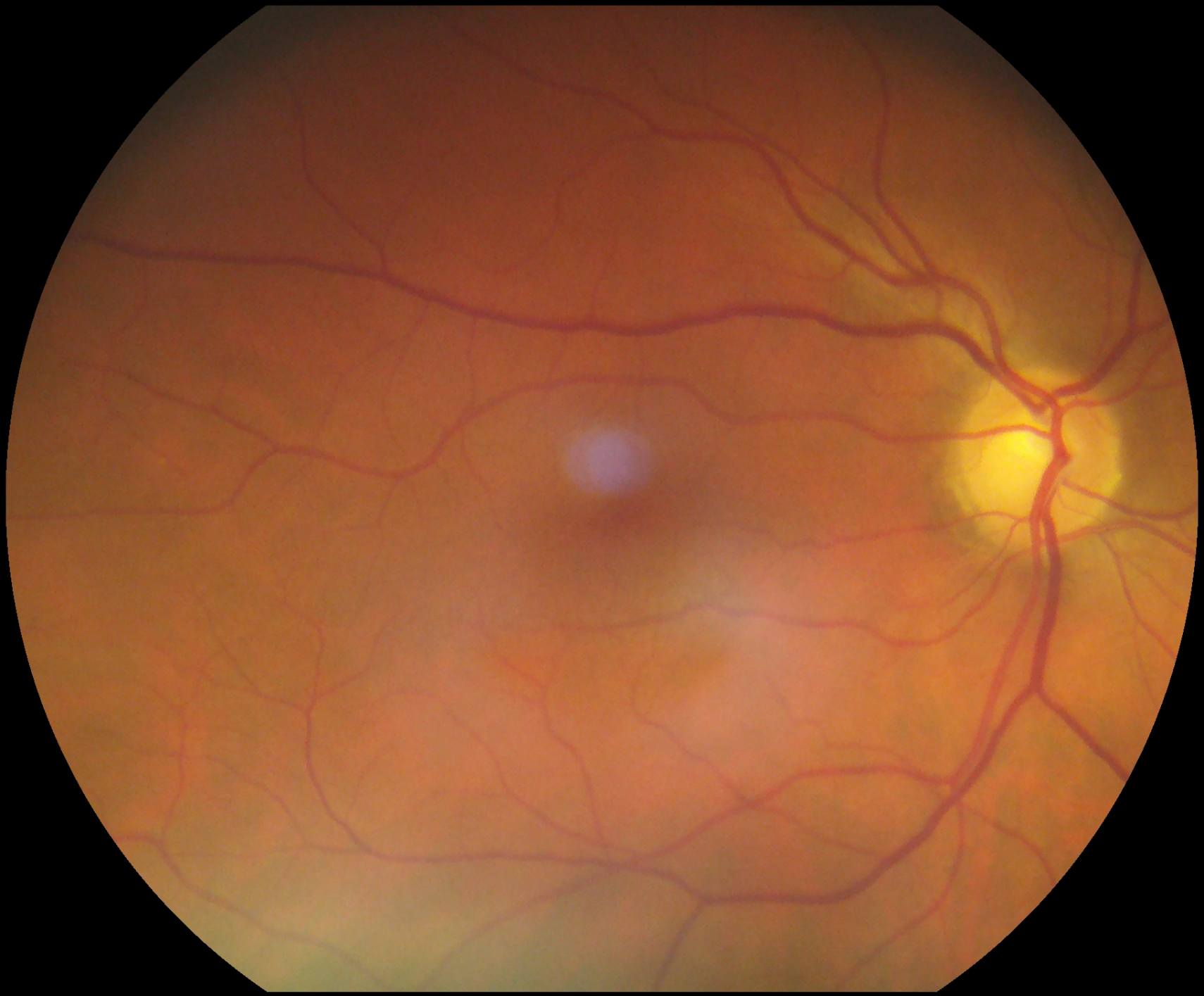
eGFR >90mL/min/1.73 m2

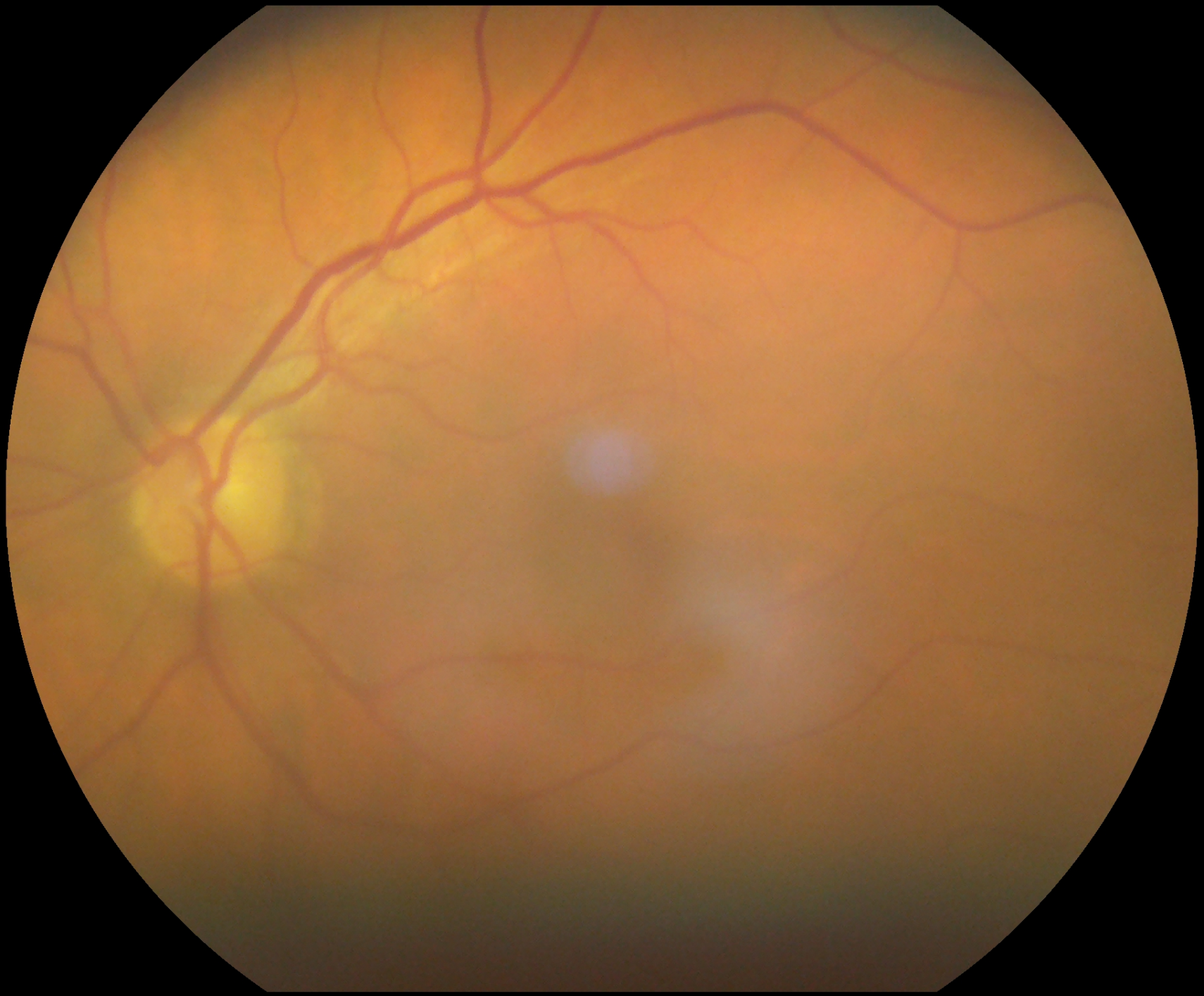
uACR 1.7 mg/mmol

Feet normal

ABI normal

Retina normal





The journey

THE PROGRESSION OF DIABETES

Age (yrs)	Year	Weight (kg)	Height (cm)	BMI
49	2005	89	173	29.9
50	2006	94	173	31.4
54	**2010**	**99**	**173**	**33.1**
62	2018	106	173	35.4
63	2019	115	173	38.4

Weight progression

Date Collected			2 Dec 15	11 Mar 16	20 Jun 16
Fasting status			Fasting	Fasting	Fasting
Serum	(3.4-5.4)	mmol/L	**7.9**	**8.3**	**8.3**
Chol	(3.9-5.2)	mmol/L	**3.7**	**2.9**	**3.2**
Trig	(0.5-1.7)	mmol/L	**2.1**	1.5	**3.1**
HDL	(1.0-2.0)	mmol/L	1.0	**0.8**	**0.8**
LDL	(1.5-3.4)	mmol/L	1.7	**1.4**	**1.0**
Non-HDL	(< 3.4)	mmol/L	2.7	2.1	2.4
Chol/HDL	(< 5.0)		3.7	3.6	4.0

HbA1c history

Date	A1c
18-Feb-13	5.9
15-Jul-13	6.2
03-Apr-14	6.4
14-Jul-14	6.8
03-Feb-15	6.8
20-Jul-15	7.2
03-Dec-15	7.3
12-Mar-16	7.2
27-Jun-16	7.3

STOP RULE!

BEFORE WE ESCALATE THERAPY…

STOP RULE!

- Adherence
- Motivation
- Patient education
- **Lifestyle issues – Diet & Exercise**
- Drug interaction
- Intercurrent infection
- Secondary causes – pancreatic pathology
- Have we excluded T1D

Lifestyle issues are as **important** in **early** as well as **advanced** diabetes

Diet

Carbohydrate intake

Regular exercises

Aerobic

Resistance

Weight loss

Low calorie diet option

Bariatric surgery in appropriate patient

Issues to consider before escalating treatment

- HbA1c target
- Symptomatic hyperglycaemia
- ASCVD risk
- Heart Failure risk
- Renal impairment
- Weight gain risk
- Hypoglycaemia risk
- Cost/PBS

For Anthony:

- **HbA1c target (7%)**
- Symptomatic hyperglycaemia
- **ASCVD risk**
- **Heart Failure risk**
- Renal impairment
- **Weight gain risk**
- Hypoglycaemia risk
- **Cost/PBS**

Anthony's current issues

GLYCAEMIC CONTROL

(HBA1C 8.6%)

BP CONTROL

(149/65)

LIPID CONTROL

(LDL 2.7 MMOL/L)

DIET UNKNOWN PROB HIGH IN CARBS

ARTHRITIS

FATTY LIVER (MILD)

OVERWEIGHT

NO EXERCISE

Given

Increase statin

Tighter BP control – ACE inhibitors/ARB?

Lifestyle – diet and exercise

Adherence checking

Vote

GO TO MENTI.COM AND USE CODE 56 73 82

Question 1: What is Anthony's HbA1c target?

Go to menti.com and Use code 56 73 82

6.0-6.5%

6.5-7.0%

7.0 – 8.0%

>8.0%

Doesn't matter – too late now

Question 2: Glycaemic control options

Go to menti.com and Use code 56 73 82

- More diet and exercise
- Increase dose of current medications
- Add sulphonylurea (e.g. diamicron MR)
- Commence GLP1-RA
- Commence insulin therapy
- Refer to endocrinologist

What can help us make a decision?

MORE INFORMATION NEEDED

Self monitored blood glucose

SMART
MONITORING –
LESS PAIN
MORE BENEFITS

Before HbA1c 8.5%	Self - monitored blood glucose (mmol/L)								
	Breakfast		Lunch		Dinner		Before Bed	Overnight	Comments
	Before	After	Before	After	Before	After			
Day 1	9.1	12.8	10.0	10.9	10.1	12.6	11.2		
Day 2	9.5	11.4	10.2	11.7	9.7	12.5	10.9		
Day 3	9.3	12.7	11.7	12.6	11.1	12.7	10.8		

Comments?

Question 3: Glycaemic control: options now?

Go to menti.com and Use code 56 73 82

More diet and exercise

Increase dose of current medications

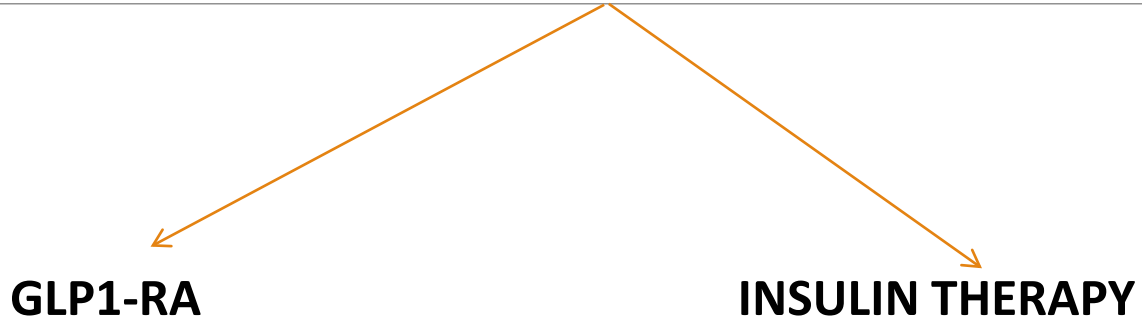
Add sulphonylurea (e.g. diamicron MR)

Commence GLP1-RA

Commence insulin therapy

Refer to endocrinologist

Starting injectables



Pros and cons

GLP1-RA

Pros

- Weight loss, Appetite reduction
- CV neutral or benefits
- Sustained HbA1c benefits
- No significant hypoglycaemia

Cons

- Nausea
- Limited potency
- May not be suitable in adv T2D

INSULIN

Pros

- Potent
- Predictable hypoglycaemic action
- Suitable at any stage of T2D

Cons

- Potential **weight gain**
- Potential hypoglycaemia

Injectable therapy

WHAT ARE THE BARRIERS?

Barriers to injectables

PATIENT FACTORS	PHYSICIAN FACTORS
Needle phobia	Hypoglycaemia worries
Hypoglycaemia risk	**Weight gain**
Weight gain	Treatment complexity
Treatment complexity	“Lack of benefit”
“End of the road”	“Too late”
Failure	Knowledge gap
Death	Inertia

Commenced Exenatide 2mg QW (Bydureon®) every Sunday
One month later…

	Self - monitored blood glucose (mmol/L)								Comments
	Breakfast		Lunch		Dinner		Before Bed	Overnight	
	Before	After	Before	After	Before	After			
Day 1	7.5	7.9							
Day 2			6.7	7.2					
Day 3	7.0	7.8							
Day 4					6.8	8.5	8.0		
Day 5	6.8	7.2							
Day 6			6.8	7.2					
Day 7					6.5	8.4	7.8		

And lost 2kg of body weight

6 months later…

	Self - monitored blood glucose (mmol/L)								
	Breakfast		Lunch		Dinner		Before Bed	Overnight	Comments
	Before	After	Before	After	Before	After			
Day 1	6.1	6.3					7.8		
Day 2	5.9	6.4							
Day 3			6.0	6.9					
Day 4					5.8	8.2	7.6		
Day 5	6.0	6.7							
Day 6			5.8	6.7					
Day 7					6.1	7.8	7.2		

And lost 6 kg of body weight

Date Collected	: 09/10/2018	15/05/2018	12/12/2017	31/08/2017		Current
HbA1C	: 6.8 *	7.7 *	7.6 *	7.1 *	%	(<6.1)
GHB	: 51 *	61 *	60 *	54 *	mmol/mol	(<43)

Latest Findings

Examination:

BP 135/71 mmHg

Weight 102 kg

Height 170 cm

BMI 35.3 kg/m^2

Laboratory results:

Fasting BSL 6.2 mmol/L

Total Chol 4.1 mmol/L

Trigs 1.4 mmol/L

HDL 1.0 mmol/L

LDL 1.8 mmol/L

HbA1c 6.8%

uACR 2.1

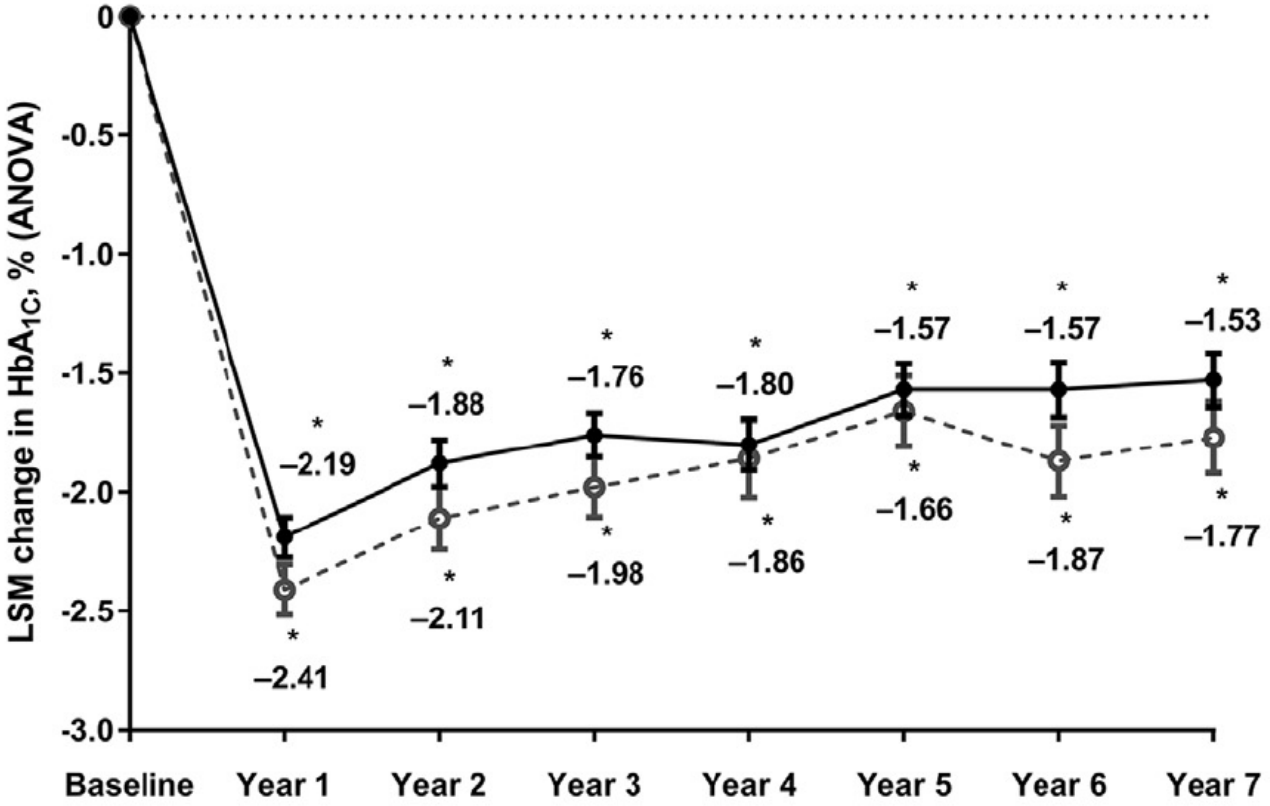
Is this sustainable?

SWIMMING AGAINST THE TIDE

DURATION 1 TRIAL

- Exenatide QW 2mg weekly vs Exenatide 10 microg bd 30 weeks
- Followed by Exenatide QW weekly continued for duration of 7 years
- Sustained reduction of HbA1c at **7 years** (average -1.53% from baseline)
- 50% patients required no additional glucose lowering medications
- Significant improvements in
  - Body weight (av. -6.5kg)
  - BP
  - Lipids

A. Philis-Tsimikas, C.H.Wysham, E. Hardy, et al., Efficacy and tolerability of exenatide once weekly over 7 years in patients with type 2 diabetes: An open-labe..., Journal of Diabetes and Its Complications J Diab Complications 2018



HbA1c over 7 years

Pleotropic effects of GLP1-RA

GLP1-RA prevents gluco-lipo-toxicity related apoptosis of beta cells in animal studies:

Wang Q, et al. Diabetologia (2004) 47:478–87.

Miao XY, et al. Peptides (2013)

Buteau J, et al. Diabetes (2001) 50:2237–43.

Lifestyle issues are as important in early as well as advanced diabetes

Diet

Carbohydrate intake

Regular exercises

Aerobic

Resistance

Weight Mx

Low calorie diet option

Bariatric surgery in appropriate patient

Managing weight

Dietitian referral

Low calorie diet

Very low calorie diet

Saxenda injections

Bariatric surgery

In summary

T2D is a progressive disease with gradual deterioration of beta cell function

In many patients, over time with gradual demise of beta cells, oral therapy will fail. HbA1c deteriorates during that time.

When oral therapy fail, often injectable therapy is required to get patient's HbA1c to target

GLP1 agonist is a good option in patients who develop oral failure

Factors to consider when choosing too escalate treatment

- Individualised glycaemic targets
- Cardiovascular benefits
- Renal benefits
- Glucose lowering potency
- Weight loss potential
- Hypoglycaemia risk
- Adherence
- Needle load
- Age
- Costs

Thank you