Masterclass PCDS 2025

? Working away from the guidelines

Learning outcomes

Prescribing

De-Prescribing

What influences prescribing ?

Guidelines

- NICE
- EASD
- ADA
- ABCD
- UKK
- BHF

Failing of current guidelines ?

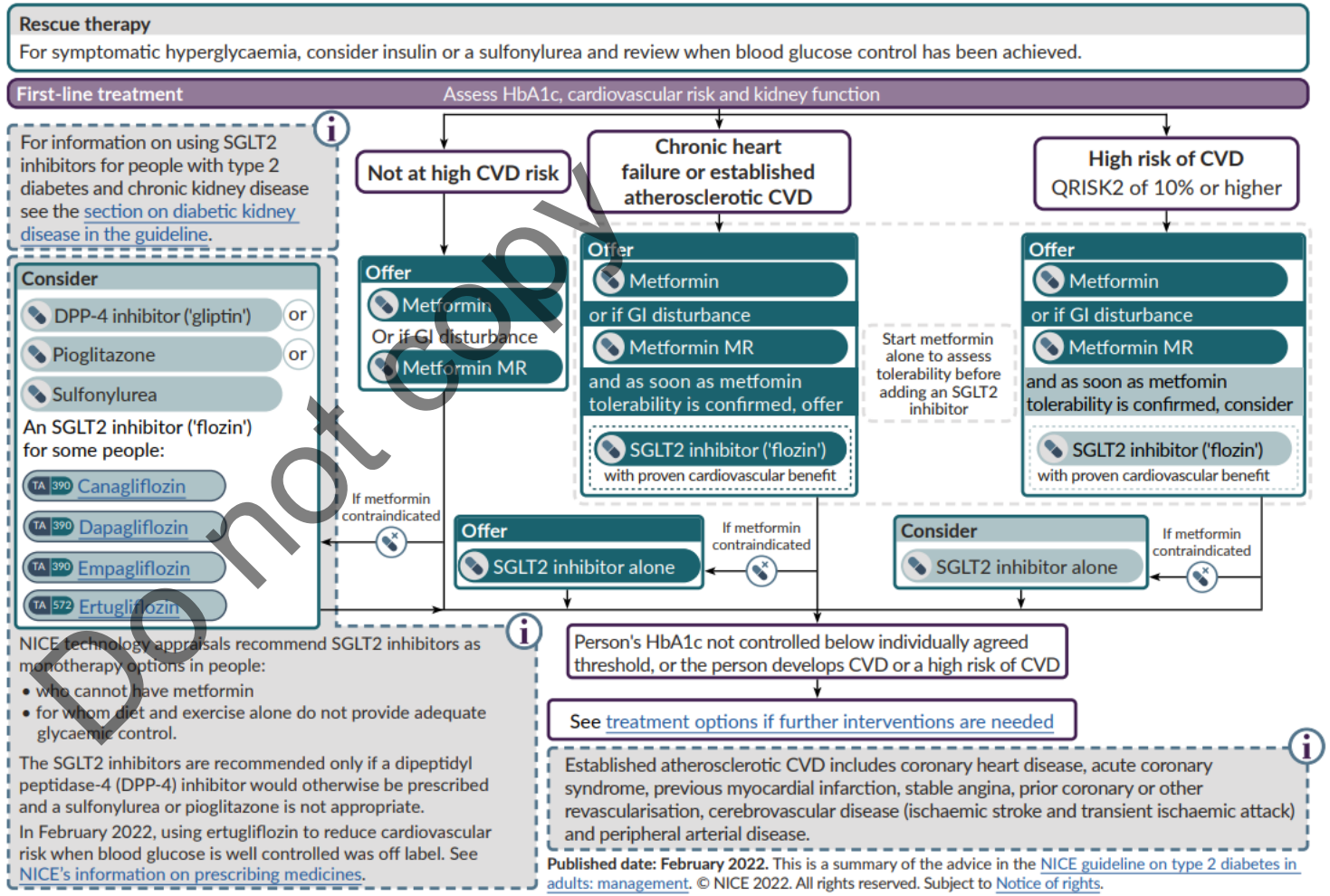
Out of date with evidence

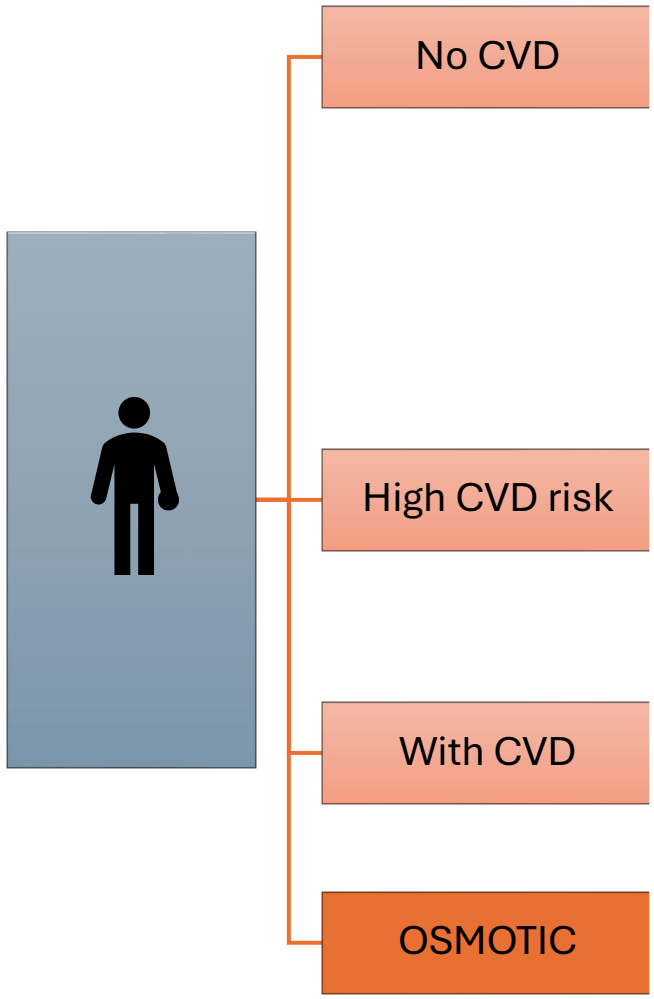
Not all encompassing

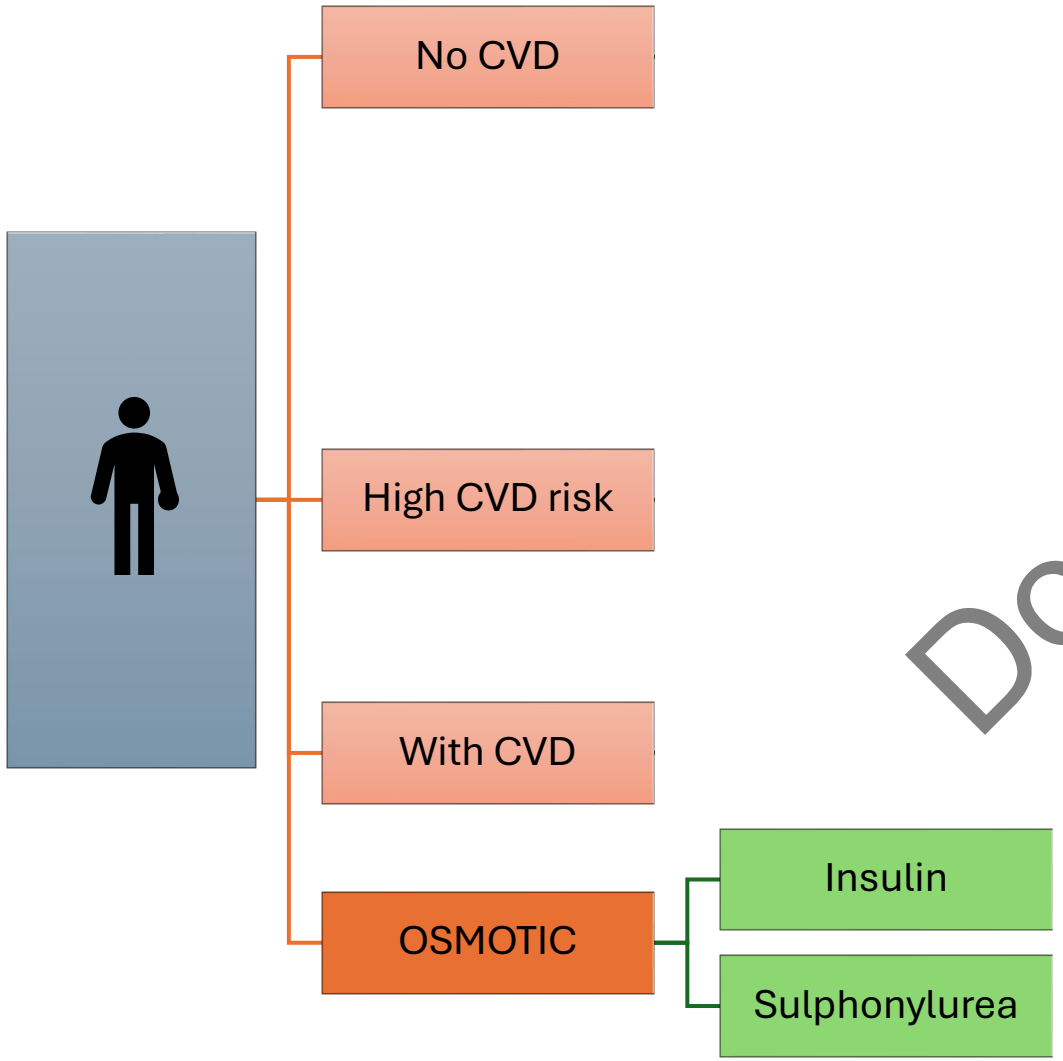
- People with diabetes may not fit criteria (Atypical Type 2/ presentations)
- Co-morbidities
  - Gastro-intestinal
  - Mental health
  - Ca-Re-Me-L
  - Frailty
  - Other therapies
- Compliance and demands
- Fertility

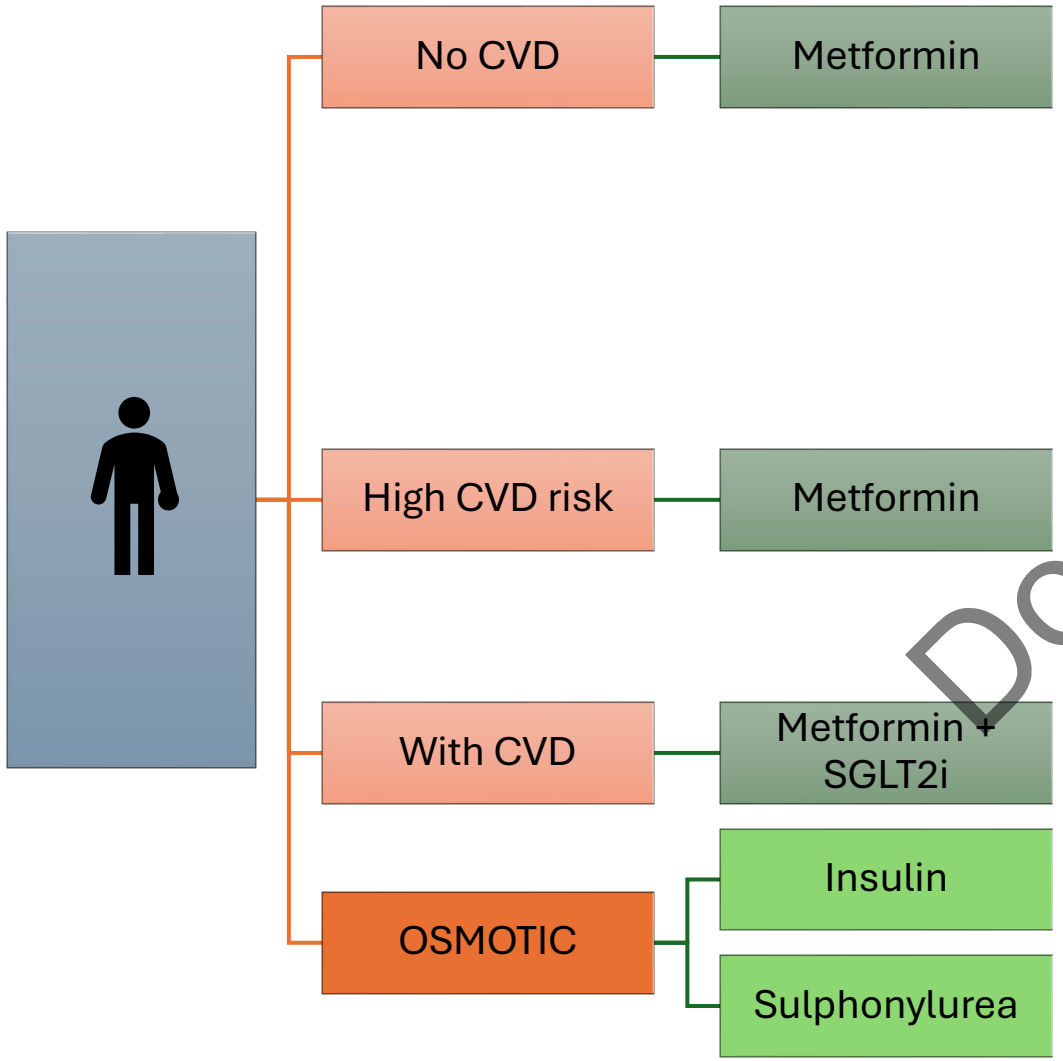
Support intensification but not reduction / de-prescribing

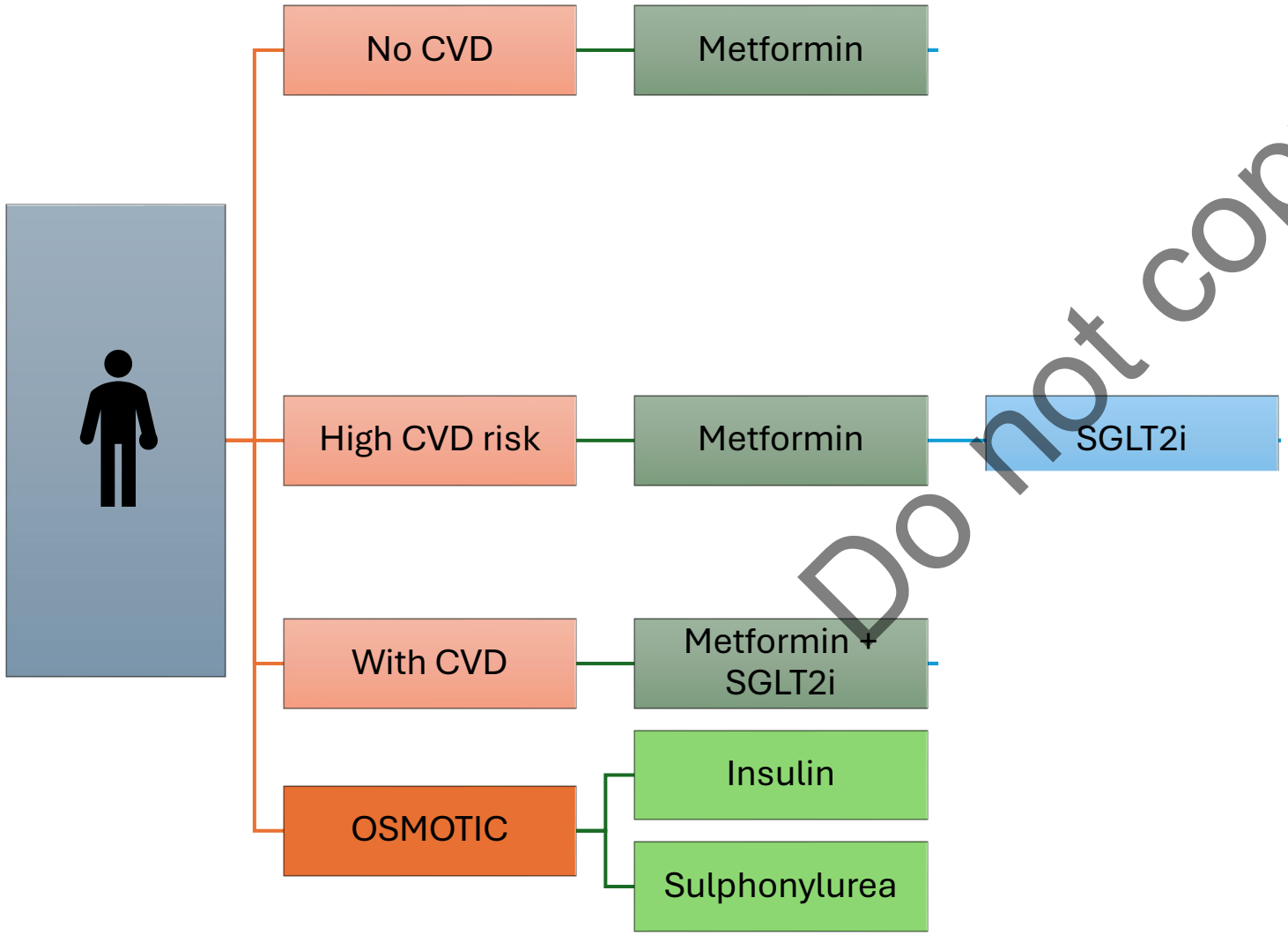
Choosing First Line Therapy






No CVD
High CVD risk
With CVD
OSMOTIC
Insulin
Sulphonylurea


No CVD
Metformin
High CVD risk
Metformin
With CVD
Metformin + SGLT2i
OSMOTIC
Insulin
Sulphonylurea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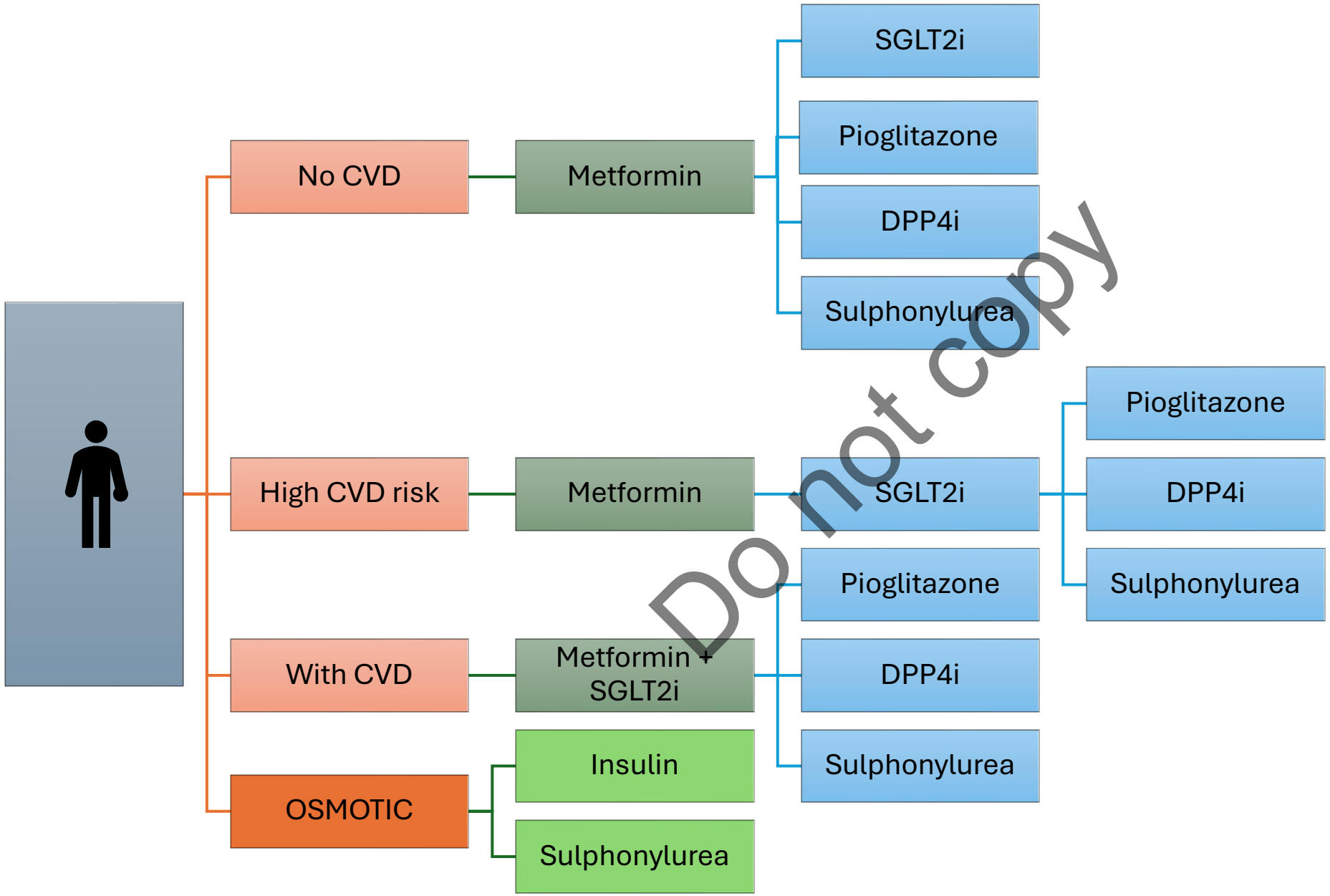
No CVD
Metformin
SGLT2i
Pioglitazone
DPP4i
Sulphonylurea
High CVD risk
Metformin
SGLT2i
Pioglitazone
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Sulphonylurea
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Insulin
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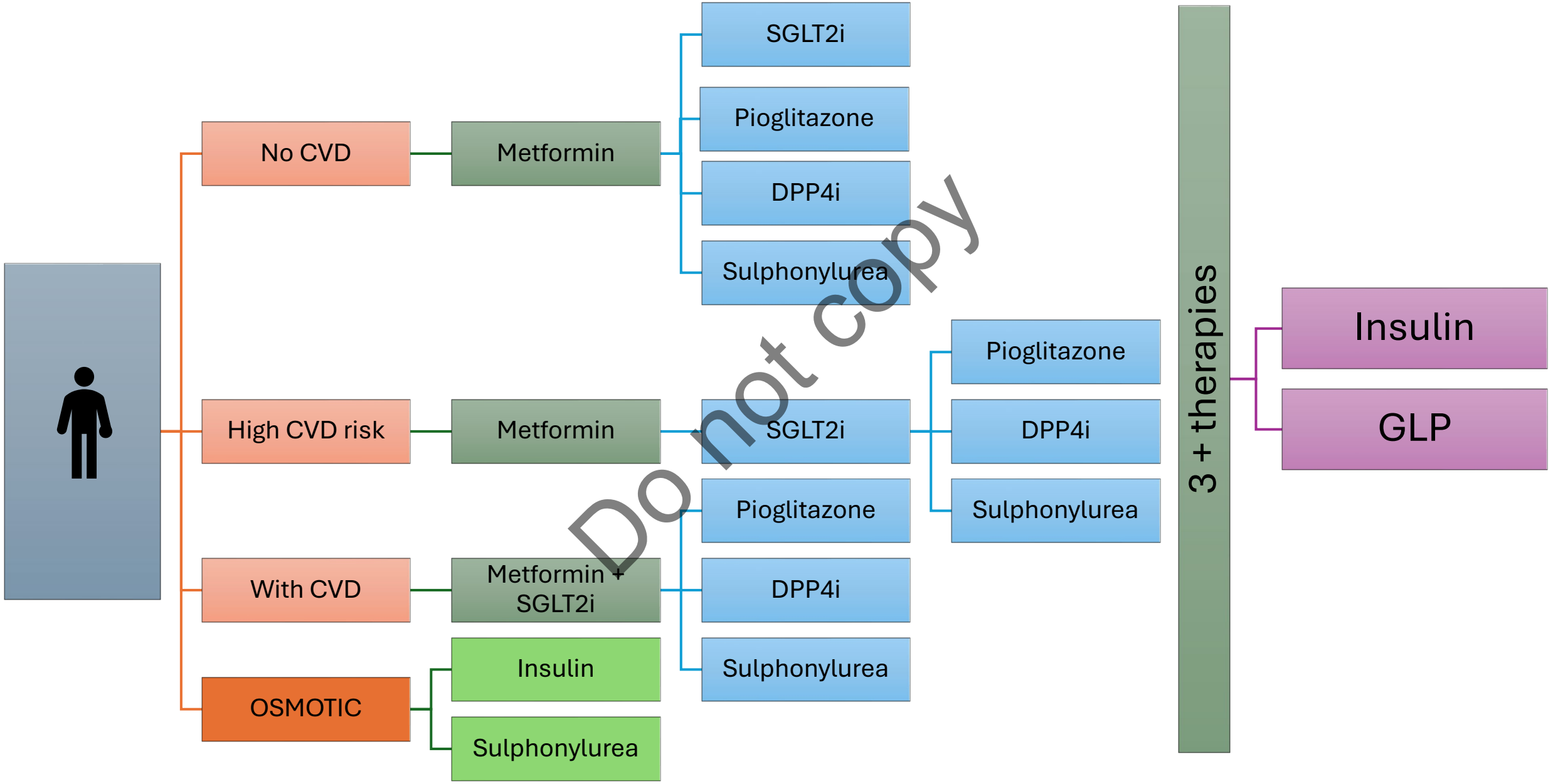
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Metformin
SGLT2i
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Sulphonylurea
With CVD
Metformin + SGLT2i
Pioglitazone
DPP4i
Sulphonylurea
OSMOTIC
Insulin
Sulphonylurea
3 + therapies
Insulin
GLP

Starting therapies

Idiosyncrasies of Medication

- Potency
- Pathophysiology
- Side effects
- Interactions
- Benefits
- Concerns
- Costs

Cost

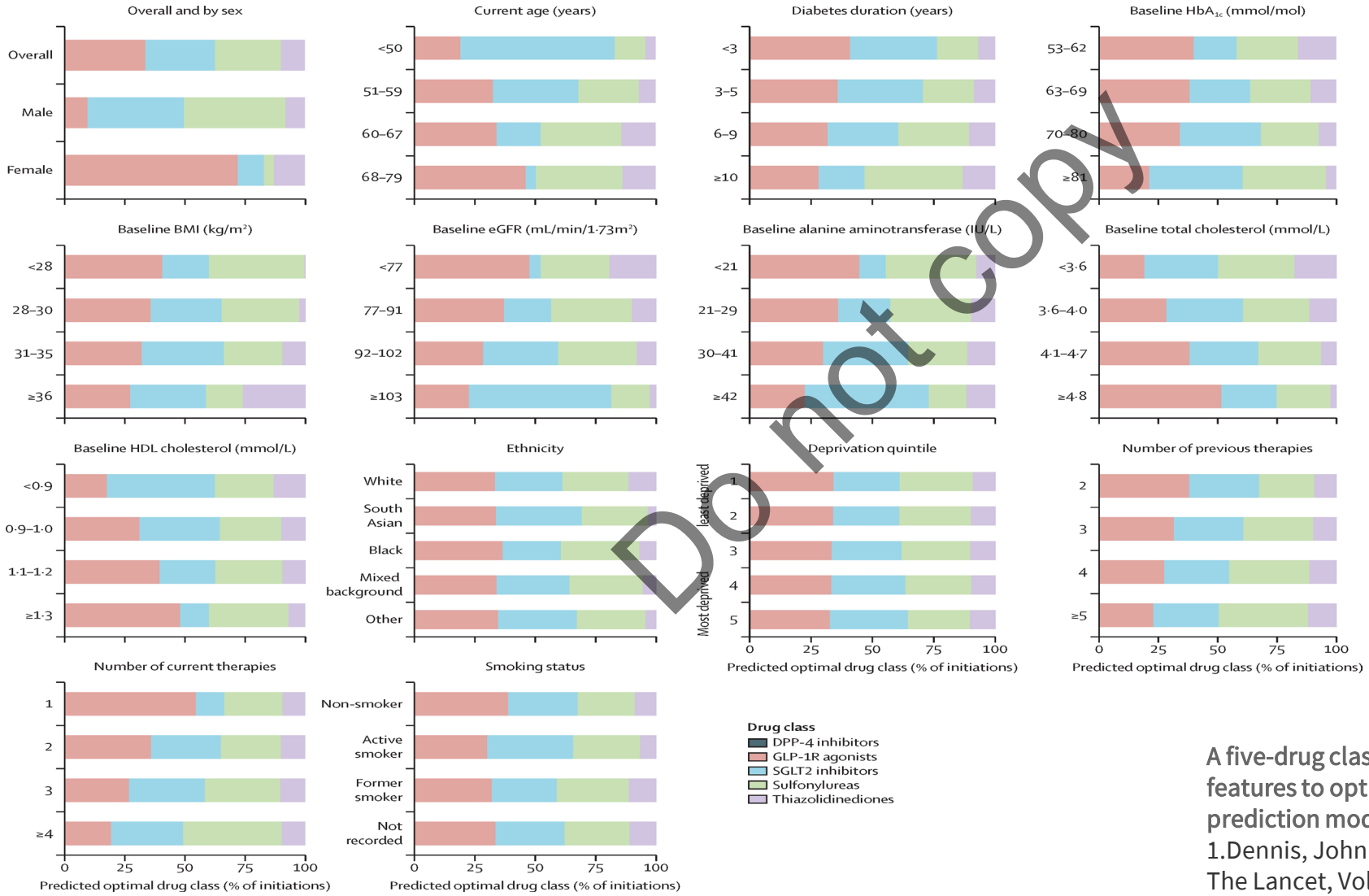
- Acquisition cost
- Cost effectiveness
- Cost of disease prevention / reduction in progression
- Cost of side effects
- Cost of monitoring
- Quality of life

Acquisition Costs

Metformin Metformin MR		£0.64 28 tabs liquid 500mg/5ml £13.64 / 100ml sachet 500mg £6.30 x 30 sachets MR £1.99 28 tabs
Gliclazide Gliclazide MR		£0.80 28 tabs (MR £1.68)
Repaglinide		0.5mg £1.54 1mg £ 2.76
Sitagliptin		£2.37 (£33.26)
Dapagliflozin / Empagliflozin / Canagliflozin		£36.59
Pioglitazone		15mg £0.97 30mg £ 1.34
GLP	Rybelsus	£78.34
	Ozempic	£73.25
	Mounjaro	£92.00 - £122.00
Insulin	Humulin I	£21.70 x5 pens
	Degludec	£46.60 x5pens
Xultophy		£95.53 x 3pens

Relative effectiveness of therapies

Predicting best therapies



A five-drug class model using routinely available clinical features to optimise prescribing in type 2 diabetes: a prediction model development and validation study
1.Dennis, John M et al.
The Lancet, Volume 405, Issue 10480, 701 - 714

Predicting best therapies

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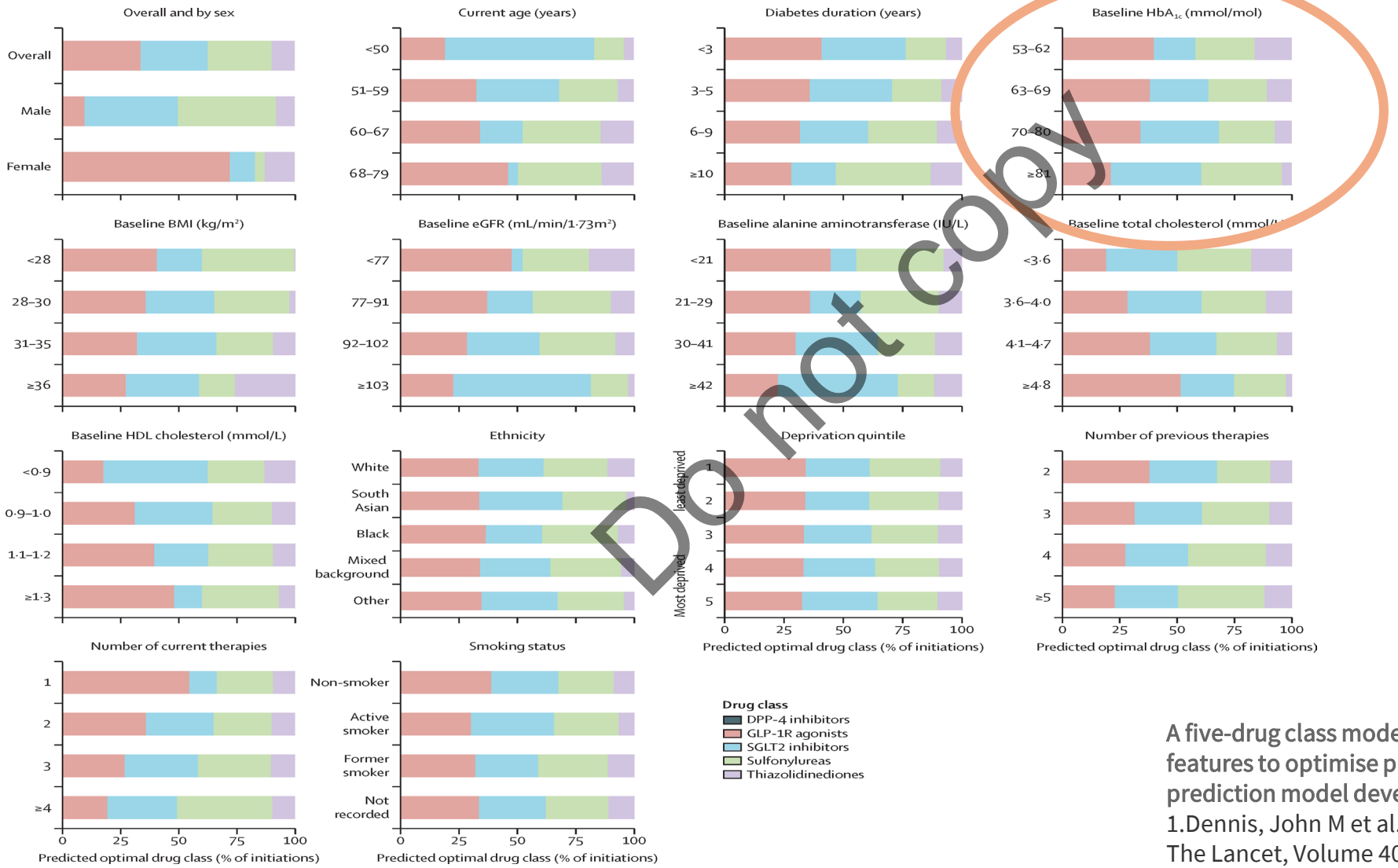

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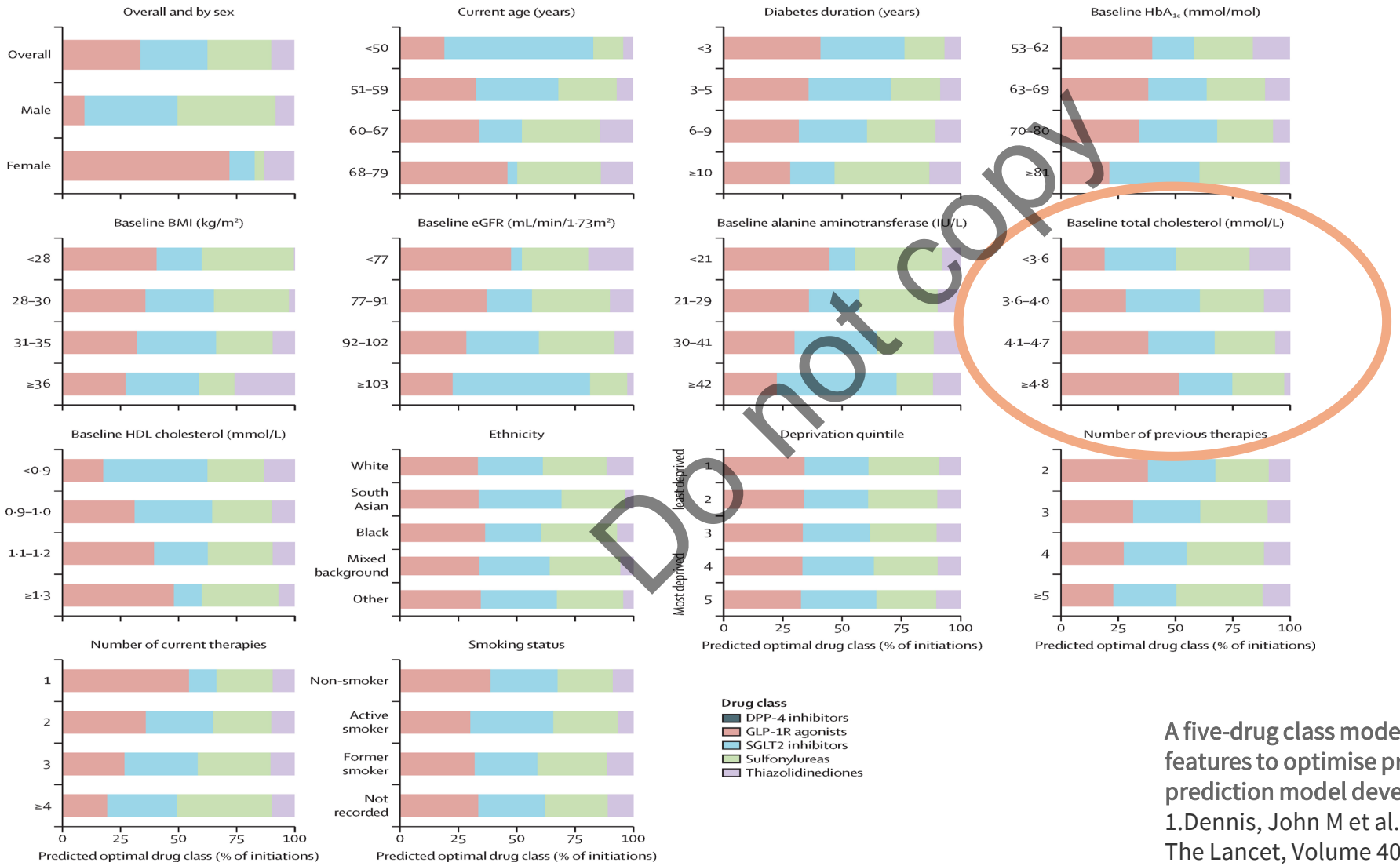

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Risks and benefits of therapies

	Benefits	Risks
Metformin	Cardiac Insulin sensitising Weight Glucose responsive	Lactic acidosis GI intolerance
Gliclazide	Glucose lowering	Hypoglycaemia Weight gain Cardiac
DPP4i	Glucose responsive	Pancreatitis URTI Heart Failure
Pioglitazone	Insulin sensitising Lipid improvement Liver benefit ? Dementia	Weight gain Fluid retention Non osteoporotic fracture Macular degeneration ?? Bladder cancer
SGLT2i	Cardiac (HFPef / HFRef) Renal Gout Weight reduction	DKS Urogenital infection Perineal ulceration (Fournier's)
GLP	Weight reduction Cardiac Hepatic Dementia	Weight loss (Gall stones) Pancreatitis Eye issues Bowel issues (Reflux / Gut transit)
Insulin		

Hypoglycaemia

- Identify those at risk

Poor appetite / erratic eating pattern

Weight loss

Therapies

- Insulin
- Oral hypoglycaemic agents

Renal impairment

Liver impairment / carcinoma

Weight

- Identify those at risk

Weight Gain

Weight Loss

Metabolic

- Identify those at risk

Lactic Acid

Ketosis

Dyslipidaemia

Renal Impairment

Liver impairment

Idiosyncrasies of Patients - Co-morbidities

- Age
- Frailty
- Liver
- Renal
- Cardiac
- Gastrointestinal
- Mental health
- Dementia
- Fertility

	**AGE**	75yrs			
	BMI	24			
	CO-MORBIDITIES	Mobility Arthritis	Cardiac MI 4yrs ago	CKD Prostatitis	
	DURATION	>10yrs			**Archie**
	EMPLOYMENT	Retired Driver			Gliclazide 80mg bd Metformin 1g bd Atorvastatin 40mg Furosemide 40mg Ramipril 10mg
	FAMILY	married			
	GOALS	Carer for wife	Hectic life		
	SYMPTOMS	none			HbA1c 88mmol/mol eGFr 45
	CV Risk	BP 110/60 Chol 3			

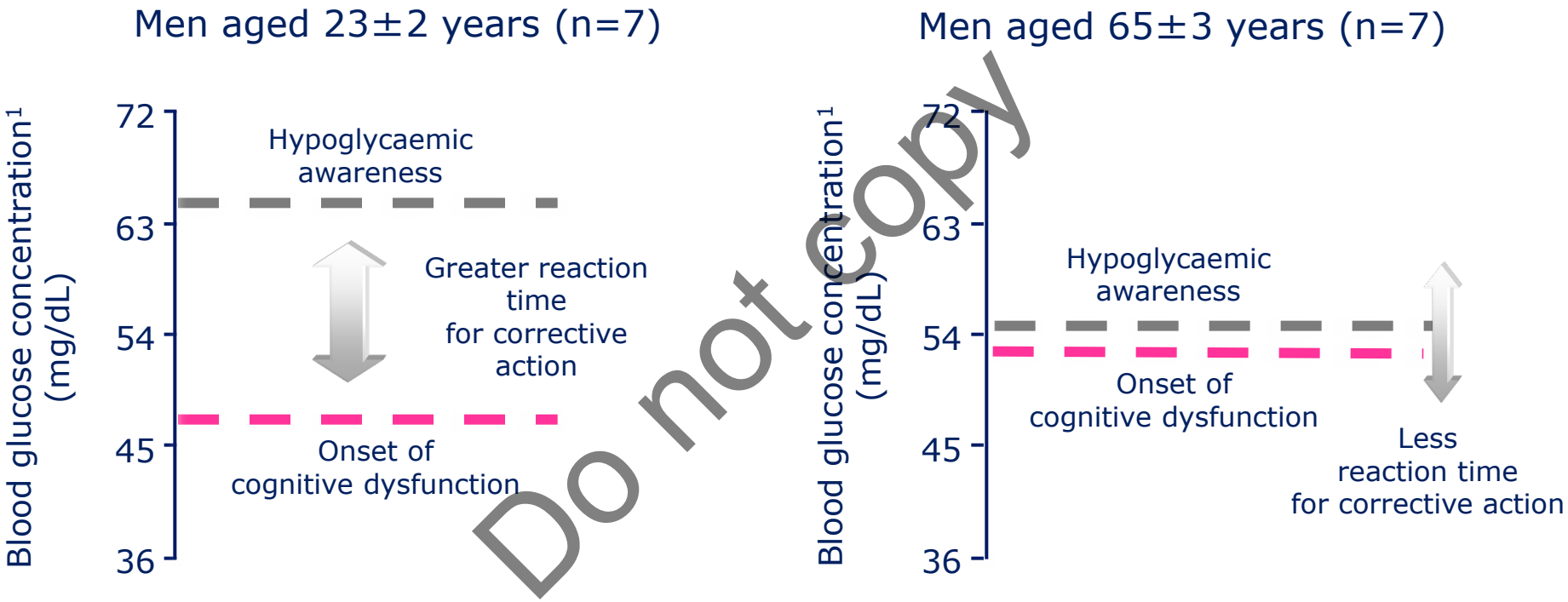
	AGE	75yrs			
	**BMI**	19			
	CO-MORBIDITIES	Mobility Arthritis	Cardiac Heart failure	CKD	
	DURATION	>10yrs			**Annie**
	Nursing Home				Novomix 6units / 4 units Atorvastatin 40mg Furosemide 40mg Ramipril 10mg Bisoprolol 1.25mg
	FAMILY	widow			
	CONCERNS	Frequent falls and declining interaction and cognition			
	SYMPTOMS	none			HbA1c 42mmol/mol eGFr 30-45
	CV Risk	BP 115/60 Chol 3			

Elderly

- Polypharmacy
- Interactions
- compliance

- Renal impairment
- Liver impairment
- Co-morbidities

Thresholds for hypoglycaemia symptoms vary with age[1,2,*]



With increasing age, potential reaction time between awareness and onset of symptoms is decreased, contributing to an increased risk for asymptomatic hypoglycaemia and greater susceptibility to cognitive impairment[1,2,*]

*Based on data in patients without diabetes with no family history of diabetes.

1. Zammitt NN, Frier BM. *Diabetes Care* 2005;28:2948–61;
2. Matyka K *et al. Diabetes Care* 1997;20:135–41

	AGE	25yrs	
	BMI	34	
	**CO-MORBIDITIES**	PCOS Gall stones	
	DURATION	<3yrs	**Jane**
	EMPLOYMENT	Office 9am-5pm	Diet
	FAMILY	married	
	GOALS		
	SYMPTOMS	none	HbA1c 68mmol/mol
	CV Risk	BP140/80 Chol 4	

	AGE	25yrs	
	BMI	34	
	**CO-MORBIDITIES**	PCOS Gall stones	
	DURATION	<3yrs	**Jane**
	EMPLOYMENT	Office 9am-5pm	Diet Metformin 1g bd
	FAMILY	married	? Weight management
	GOALS		
	SYMPTOMS	none	HbA1c 62 mmol/mol
	CV Risk	BP140/80 Chol 4	

Pre-pregnancy

- Contraception
- Fertility
- Therapies / safety

Pre-pregnancy

Contraception

- Safe and effective contraception
- Effects on efficacy

Fertility

Therapies / safety

GLP and Oral Contraceptives

Drug	Interaction and recommendations
Tirzepatide (Mounjaro)	Decrease Bioavailability barrier methods recommended for 4 weeks after initiation and dose increase
Semaglutide (Ozempic)	No effect on bioavailability of OCP
Liraglutide (Victoza)	No effect on bioavailability of OCP
Dulaglutide (Trulicity)	No effect on bioavailability of OCP
Exenatide (Bydureon)	Diminishes therapeutic effect of OCP
Lixisenatide (Adlyxin)	Diminishes therapeutic effect of OCP – take OCP at least 1 hour prior to injection or at least 11hours after

Skelly JW etal The impact of Tirzepatide and GLP1 agonists on oral contraception J Am Pharm Assoc (2003)2024;64(1)204-211
Mounjaro Prescribing information. Indianapolis, Lilly USA LLC November 2024

Pre-pregnancy

Contraception

Fertility

- Change in fertility
- Weight loss
- Action of medication

Therapies / safety

Pre-pregnancy

Contraception

Fertility

Therapies / safety

- Teratogenicity

	AGE	50yrs		
	BMI	32 (40)		
	CO-MORBIDITIES	Recurrent thrush	Hepatic steatosis	
	**DURATION**	<8yrs		Susan
	EMPLOYMENT	Dinner Lady 10am-3pm	Driver	Metformin 1g bd Dapagliflozin 10mg Semaglutide 1mg
	FAMILY	married		
	GOALS	Hectic life		Malb/Creat.= 5 eGFr = 87
	SYMPTOMS	none		HbA1c 38mmol/mol
	CV Risk	BP150/80 Chol 4 Tg 3		ALT 46mmol/l AlK Phos 100mmol/l

Stopping therapies

Stopping therapies

When therapies have shown no benefit

- No clinical response to treatment

When targets not achieved

- Partial response to treatment

NICE Guidance on GLP-1

NICE suggests that **if triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated, HCPs should consider combination therapy with metformin, a sulfonylurea and a GLP-1 RA using starting and stopping criteria based on weight**

Starting criteria

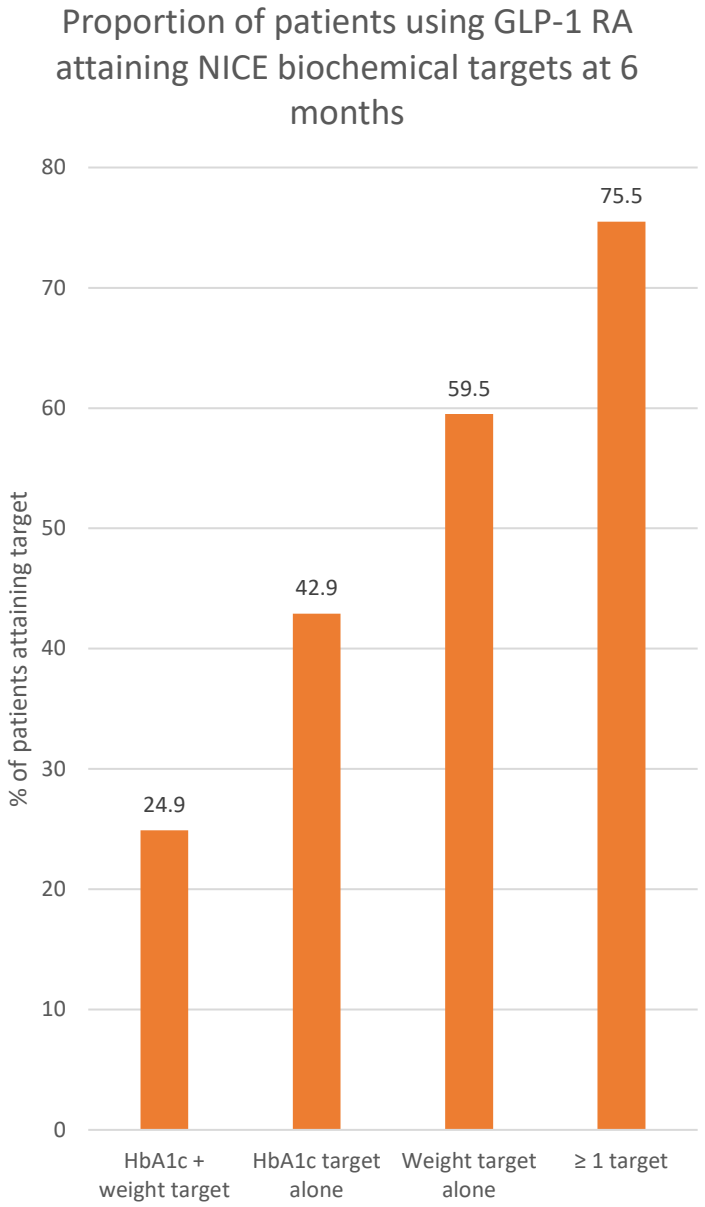
- Body mass index (BMI) ≥ 35kg/m^2 (adjust for ethnicity) and specific psychological or other medical problems associated with obesity
- BMI <35kg/m^2 when insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities

Stopping criterion

- Only continue GLP-1 RAs if the person has had a beneficial metabolic response: reduction of ≥11mmol/mol (1.0%) in HbA_{1c} and a weight loss of ≥3% of initial body weight in 6 months

Only a quarter of patients who start a GLP-1 RA achieve both NICE targets

- In a retrospective study of 1123 people, **68% completed 6-months treatment with GLP-1 RA;** of those with a weight and HbA_{1c} record at 6 months **only 25% achieved both NICE criteria for a beneficial metabolic response**



Stopping therapies

When targets have been achieved

Weight regain post GLP therapies

After 36 weeks of open-label maximum tolerated dose of tirzepatide (10 or 15 mg), adults (n = 670) with obesity or overweight (without diabetes) experienced a mean weight reduction of 20.9%. From randomization (at week 36), those switched to placebo experienced a 14% weight regain and those continuing tirzepatide experienced an additional 5.5% weight reduction during the 52-week double-blind period.

Meaning In participants with obesity/overweight, withdrawing tirzepatide led to substantial regain of lost weight, whereas continued treatment maintained and augmented initial weight reduction

Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity The SURMOUNT-4 Randomized Clinical Trial
Louis J. Aronne, MD[1]
JAMA. 2024;331(1):38-48. doi:10.1001/jama.2023.24945

(Regain in weight lost in 10months compared to <5 years with traditional weight loss management)

Diagnostic Criteria for Remission

HbA1c <48mmol/mol on 2 consecutive occasions 6 months apart and off all diabetes medications.

Diagnostic Criteria for Remission

HbA1c <48mmol/mol on 2 consecutive occasions 6 months apart and off all diabetes medications.

Off ALL Medication !!!

Diagnostic Criteria for Remission

HbA1c <48mmol/mol on 2 consecutive occasions 6 months apart and off all diabetes medications.

HbA1c <42mmol/mol on 2 consecutive occasions 6 months apart and only on

Metformin (for PCOS/ weight)

SGLT2 (for renal / cardiac measures)

Pioglitazone (for fatty liver disease)

or

GLP1RA (for weight / Heart / etc)

Management of Remission

- Management of remission

Prevention of relapse with medications

Maintenance of remission

Drugs After Remission Is Established

Metformin’s main action affecting glycaemic control in diabetes is to improve hepatic responsiveness to portal insulin. It is not known whether it can delay relapse .

When remission is diagnosed , therapy with metformin or other drugs not used for glycaemic indications may delay recurrence of hyperglycaemia and/or protect against progression of other cardio / metabolic harm.

How to reduce therapies

Insulin Reduction

- ? Crisis risk (DKA / HSS)

Oral therapies

- Which therapies to maintain?
  - Metformin – PCOS / Weight
  - SGLT2i – renal / cardiac protection
  - Pioglitazone – NASH
  - GLP1RA – weight maintenance / NASH / Cardiac protection

Mental Health

Mental Health

- Mental Health
  - Compliance
    - Interactions
    - Simplicity of regimen
    - Compliance therapy / lifestyle

	AGE	65yrs		
	BMI	34		
	CO-MORBIDITIES	Renal eGfr 45-60	COPD Recurrent infections	Memory issues
	DURATION	10yrs		
	**EMPLOYMENT**	Retired		
	FAMILY	single		
	GOALS	Structured education		
	SYMPTOMS	none		
	CV Risk	BP 140/80 Chol 5.5		

Anne

Metformin 1g bd
Dapagliflozin 10mg
Gliclazide 80mg bd

HbA1c 64mmol/mol

Compliance

Compliance Issues

- **Therapies**
  - Confusion / side effects / interactions
  - Timing / swallowing
- **Advice / behaviour change** – breaking habits
- **Ways to improve compliance**
  - Dosset box
  - Combination tablets
  - Reduce inappropriate therapies
  - Support (educational / social)

Over compliance

- **Sick day rules**
  - Not stopping therapies
- **Nursing home care**

Medication Refusal

Is covert medication administration appropriate and justified?

Order the importance of medication to prevent symptoms or deterioration in health (preventative medication such as aspirin and statins may not be seen as a priority)

Consider alternative preparations

- Liquids , smaller sized tablets

Consider change in regimen for fewer therapies

- Changing timing of medication dose
- Combination therapies

Combination therapies

	Metformin		DPP4i		Pioglitazone	
SGLT2	Empagliflozin	**Synjardy**	Empagliflozin + Linagliptin	**Glyxambi**		
	Empagliflozin + Metformin + Linagliptin			**Trijardy**		
	Ertugliflozin	**Segluromet**	Ertugliflozin + sitagliptin	**Stegujan**		
	Dapagliflozin	**Xigduo**	Dapaglifozin + Saxagliptin	**Otern**		
	Canagliflozin	**Invokamet**				
Pioglitazone		**Actoplus**	Alogliptin	**Oseni**		
DPP4i	Sitagliptin	**Janumet**				
	saxagliptin	**Kombglyze**				
	Linagliptin	**Lentdueto**				
	Alogliptin	**Kazano**				
Sulphonylurea	Glyburide	**Glucovance**			Glimepiride	**Duetact**
	Glipizide	**Metaglip**				

Psychological issues with prescribing

Depression

Dementia

Diabetes Distress

Diabetes Burnout

Eating Disorders

Fear

- Hypoglycaemia
- Complications / poor control
- Injection fear
- Polypharmacy

	AGE	65yrs	
	BMI	25	
	CO-MORBIDITIES	Dementia eGfr <55	
	DURATION	>10yrs	**Sandra**
	Lives in nursing EMI Home		Empagliflozin 10mg Mounjaro 7.5mg Metformin 1g MR Gliclazide 40mg bd
	**FAMILY**	married	
	CONCERNS	Frequent UTI Compliance	Malb / Creat = 35
	SYMPTOMS	none	HbA1c 58mmol/mol
	CV Risk	BP140/80 Chol 4 mmol/l	

Diabetes and Dementia

The association of diabetes and cognitive decline has been examined in prospective studies :

- Four of six studies have found an association between diabetes and cognitive decline as measured by repeated neuropsychological tests [3,4,5,6]
- Additionally , five of seven cohort studies associated diabetes with roughly doubling the overall risk of dementia

3. Gregg EW, Narayan KMV. Type 2 diabetes and cognitive function: are cognitive impairment and dementia complications of type 2 diabetes? Clin Geriatr. 2000;8:57–72.
4. Haan MN, Shemanski L, Jagust WJ, Manolio TA, Kuller L. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. JAMA. 1999;282:40–46.
5. Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, et al. Atherosclerosis Risk in Communities (ARIC) Study Investigators. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology. 2001;56:42–48.
6. Fontbonne A, Berr C, Ducimetiere P, Alperovitch A. Changes in cognitive abilities over a 4-year period are unfavorably affected in elderly diabetic subjects: results of the epidemiology of vascular aging study. Diabetes Care. 2001;24:366–370

Diabetes and Dementia

Insulin in the brain

- Insulin receptors in the brain control glucose metabolism and neuropeptides
- Insulin resistance affects brain function
  - Inflammation
  - Beta amyloid plaque formation

GLP-1 in the brain

- GLP-1 protects neuronal cells from amyloid build up

Hyperglycaemia

- Association of hyperglycaemia and cognitive decline

Vascular complication

Dementia Benefits / Harms of medicines

- Gliclazide
- Metformin
- DPP4i
- Pioglitazone
- SGLT2i
- GLP1

Terminal care

	AGE	50yrs		
	BMI	32		
	CO-MORBIDITIES	Renal eGfr 45 ACR 25	Metastatic prostate cancer	
	DURATION	10yrs		**Roger**
	EMPLOYMENT	Ex -Shift worker		Metformin 1g bd Atorvastatin 20mg
	FAMILY	married		
	**CONCERNS**	Prognosis < 12 months		
	SYMPTOMS	none		HbA1c 108mmol/mol
	CV Risk	BP 130/80 Chol 3.5		

	AGE	50yrs		
	BMI	28		
	CO-MORBIDITIES	Endometrial cancer Liver metastatic disease		
	DURATION	<8yrs		**Mary**
	EMPLOYMENT	Office 9am-5pm		Metformin 1g bd Empagliflozin 10mg Mounjaro 5mg
	FAMILY	married		
	GOALS	Structured education		
	**SYMPTOMS**	Thrush cystitis	Varicose ulcer	HbA1c 80mmol/mol
	CV Risk	BP 140/80 Chol 5.5		

Frailty / End of life

Targets

Simplification of regimens

Avoidance complications

Hyper glycaemia (DKA / HSS)

Hypoglycaemia

Skin / infection

Dehydration

Gastro-intestinal disease

GORD

Gastroparesis (Avoid GLP / ? Repaglinide)

Malabsorption (? Avoid secretalogues)

Liver impairment (Pioglitazone / GLP)

Dumping (Arcobose)

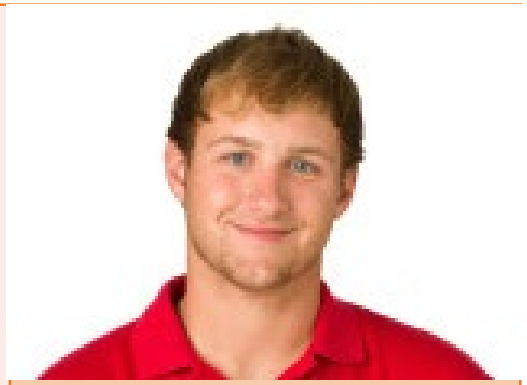
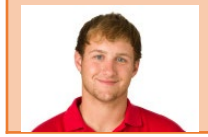
GI-Transit issues

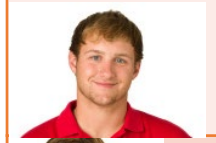
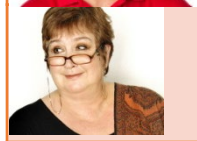
- Constipation
- Diarrhoea

Liver / renal precautions

- Brittle diabetes
- Hypoglycaemia risks
- Efficacy of therapies
- Reliability of tests (HbA1c)

Liver disease

	AGE	35yrs		
	BMI	28		
	CO-MORBIDITIES	Alcohol ++		
	DURATION	<3yrs		**Michael**
	EMPLOYMENT	Builder 8am-4pm	Driver	Metformin 1g bd
	FAMILY	single		
	GOALS	Rugby		
	SYMPTOMS	osmotic		HbA1c 78 mmol/mol ALT 125mmol/l
	**CV Risk**	BP 115/60 Chol 3		

	**AGE**	25yrs	35yrs	50yrs	65yrs	75yrs
	**BMI**	24	28	30	34	40
	**CO-MORBIDITIES**	mobility	cardiac	Renal eGfr 45-60	Renal eGfr 30-45	Renal eGfr <30
	**DURATION**	<3yrs	10yrs	>10yrs		
	**EMPLOYMENT**	Retired	Office 9am-5pm	Builder 8am-4pm	Shift worker	Taxi Driver Class 2
	**FAMILY**	single	married			
	**GOALS**	Structured education	carer	Hectic life		
	**SYMPTOMS**	none	osmotic			
	**CV Risk**	BP 140/80 Chol 5.5	BP140/80 Chol 4	BP 115/60 Chol 3	BP160/90 Chol 6 Tg 5	BP160/70 Chol 5