Birmingham and Solihull

Guidance for dosing adjustments
Type 2 Diabetes Path to remission (T2DR)

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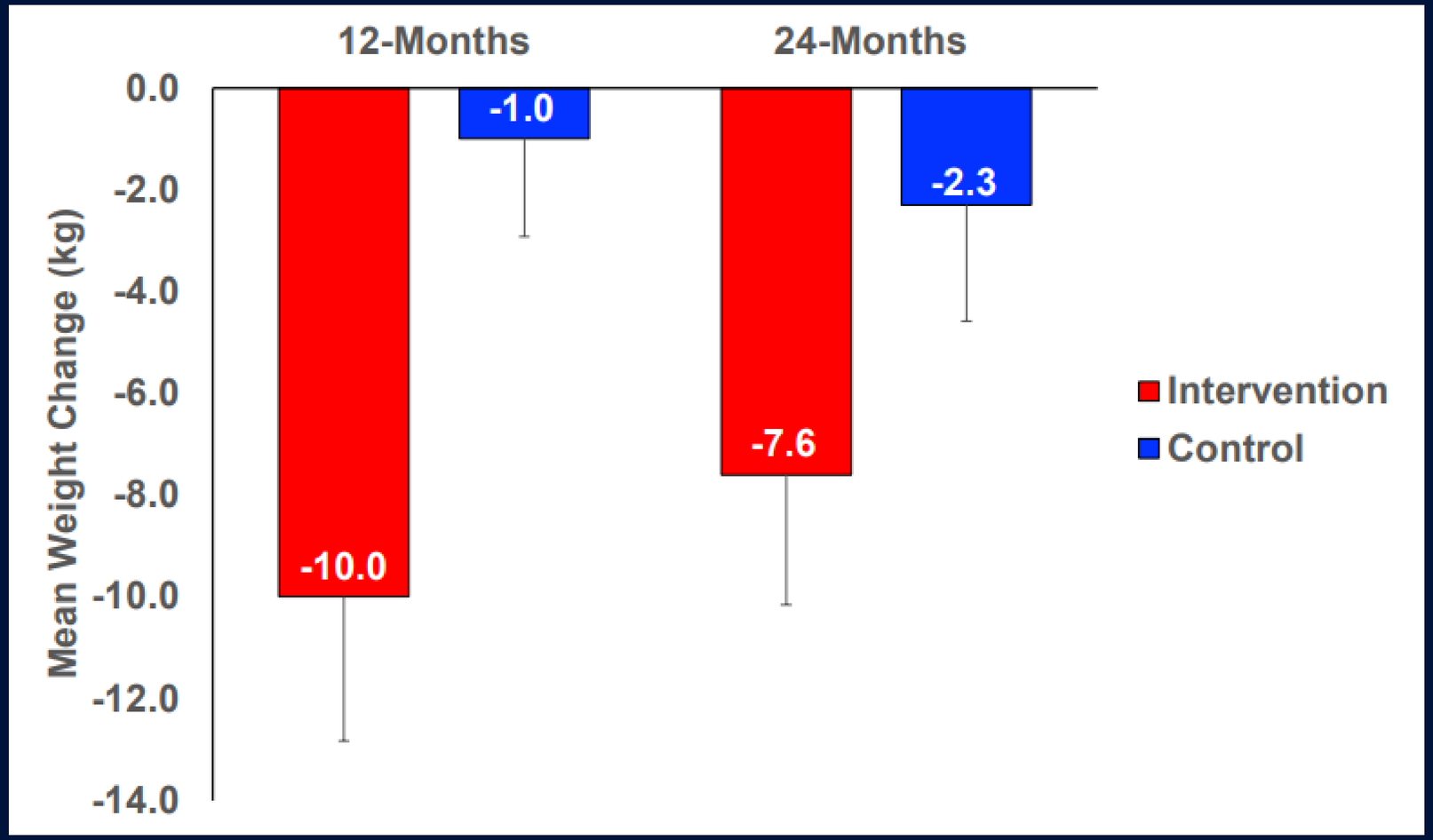
Background

- The findings of both the DiRECT trial (2017) and later the DROPLET trial (2018)
- On the first day of starting total diet replacement (TDR), all glucose-lowering agents and BP-lowering agents were stopped
- At 1 year, 46% of people in the intervention group achieved remission (as defined in the trial), compared to 4% in the control group
- Weight loss was strongly associated with achievement of remission. The 2 year data showed that 64% of people with ≥10kg loss at 2 years were in remission, compared to 29% of people with 5-10kg weight loss and 5% of people with <5kg weight loss
- While DiRECT used nurses or dieticians to provide behavioural support, the DROPLET trial (2018) showed that similar weight loss outcomes to DiRECT could be achieved using a trained workforce of non-healthcare professionals to deliver the behavioural support elements of the low calorie diet (LCD) intervention

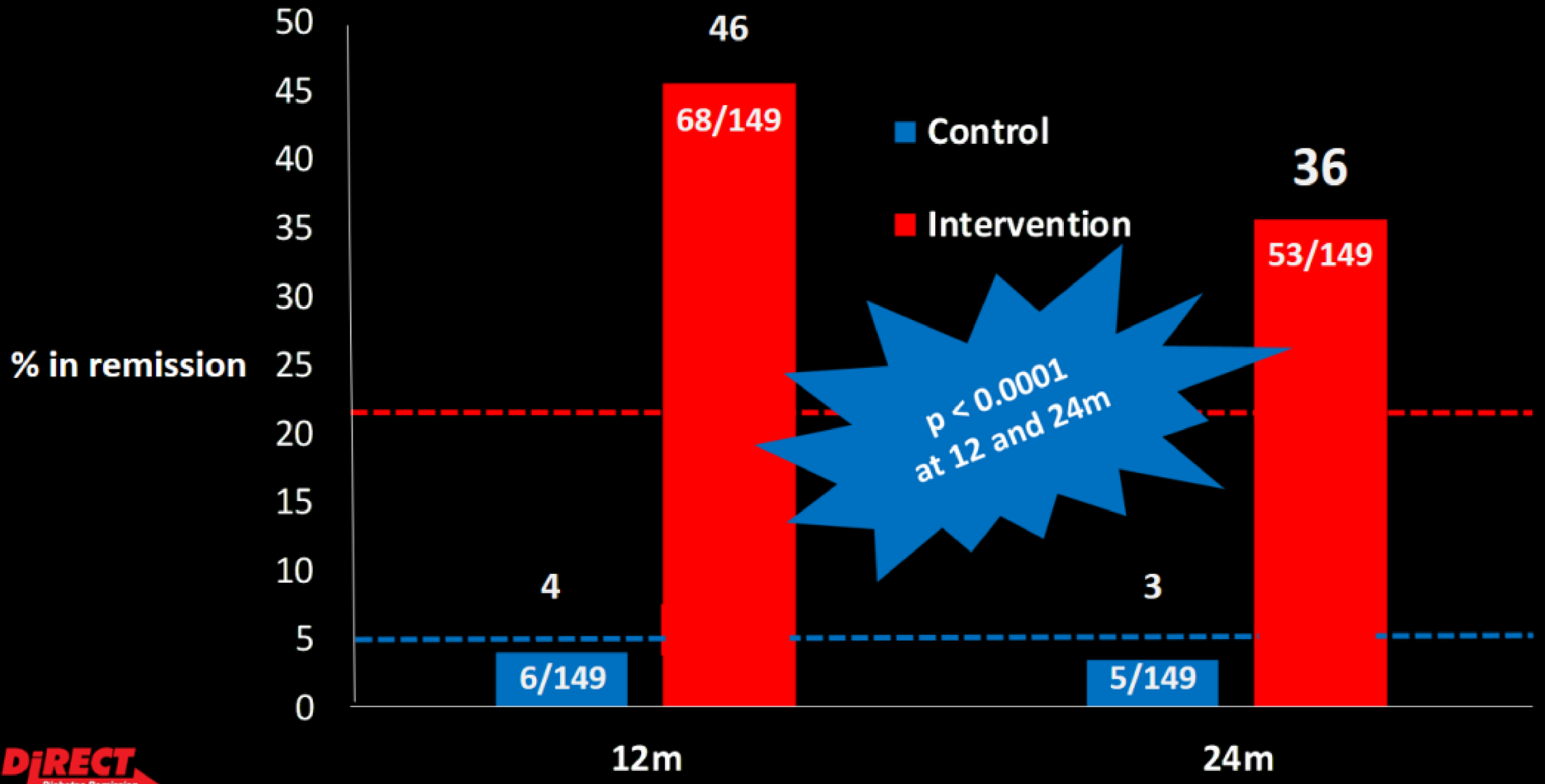
Greater weight loss 0-24months in intervention group



Lean et al, Lancet (2017)
Lean et al, Lancet Diabetes and Endocrinology (2019)

DiRECT Diabetes Remission Clinical Trial
University of Glasgow
Newcastle University
DiABETES UK CARE. CONNECT. CAMPAIGN.

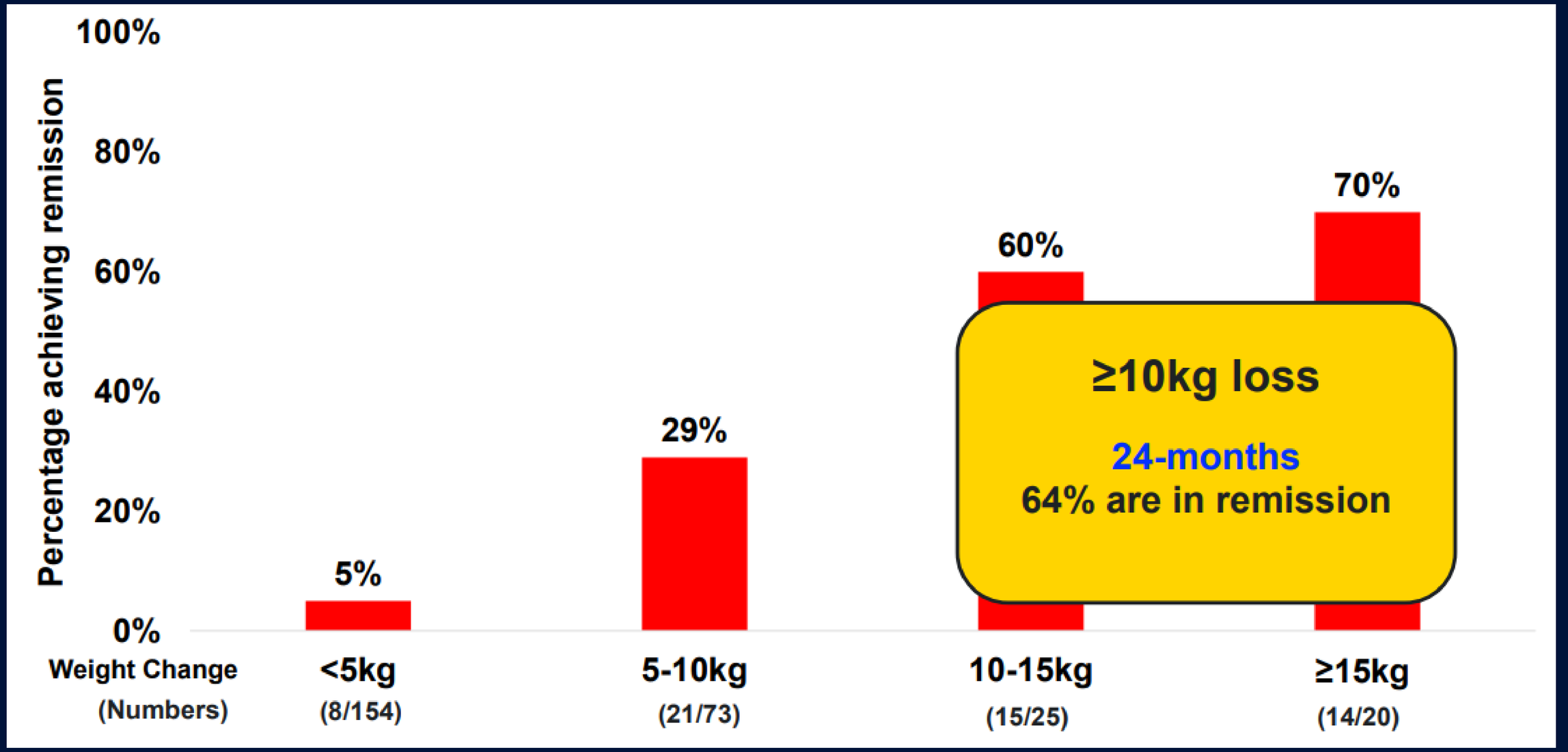
Remissions at 24 months



DiRECT
Diabetes Remission Clinical Trial

Lean ME et al *Lancet Db&End* 2019

Remissions by 24-month weight loss: entire study population



DiRECT Diabetes Remission Clinical Trial

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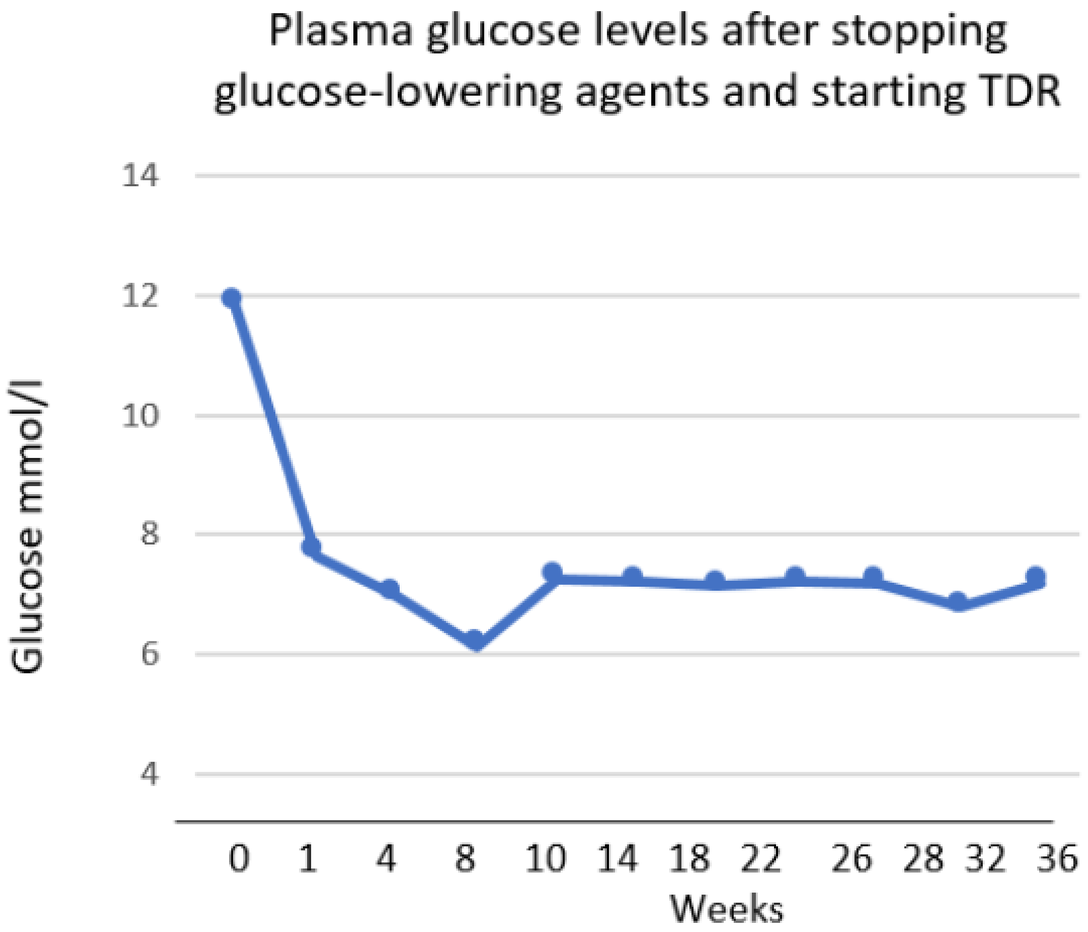
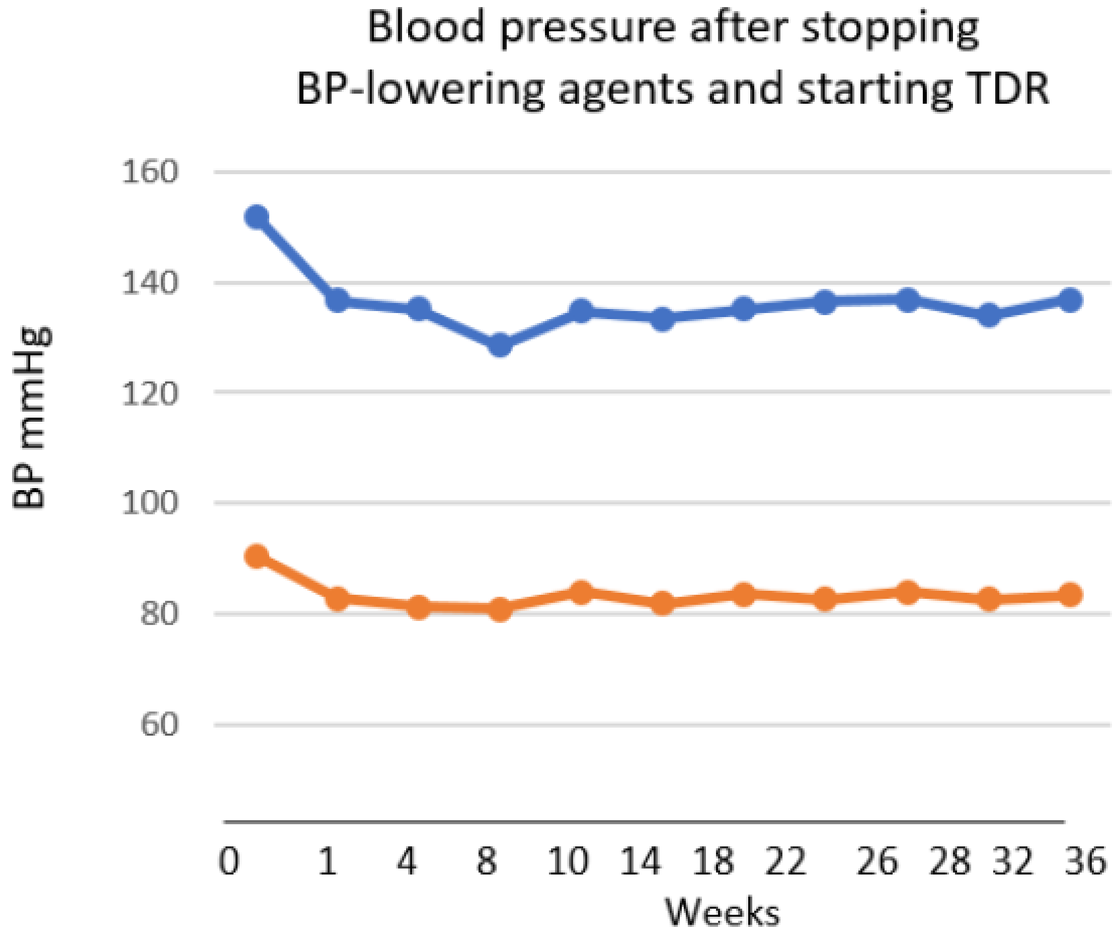
Expected blood glucose & BP changes on TDR





Medication Changes

Not all medications will need to be stopped/adjusted.

The medication adjustments recommendations outlined in this slide pack have been formulated by an Expert Advisory Group including the lead investigators of the DiRECT and DROPLET trials, consultant diabetologists and primary care clinicians.

The recommendations are designed to be safe, evidence-based and pragmatic. They do not replace clinical judgment and constitute guidance only. Clinical responsibility remains with the referring GP practice

Glucose lowering medications

Class of medication	Examples of drugs	Is this safe with TDR?
Biguanides	Metformin	Yes – safe
Sulfonylureas	Gliclazide, Glibenclamide, Glimepiride	No – risk of hypoglycaemia
Meglitinides	Repaglinide, Nateglinide	No – risk of hypoglycaemia
Thiazolidinediones	Piogliazone	Yes - safe
DPP4 inhibitors (-gliptins)	Linagliptin, Alogliptin, Sitagliptin, Saxagliptin, Vildagliptin	Yes - safe
SGLT2 inhibitors (-flozins)	Dapagliflozin, Canagliflozin, Empagliflozin, Ertugliflozin	No – risk of ketoacidosis
GLP-1 analogues (-tides)	Exenatide, Dulaglitide, Liraglutide, Lixisenatide, Semaglutide	Yes - safe
Alpha-glucosidase inhibitors	Acarbose	Yes - safe
(insulin is not included here as people treated with insulin are not eligible for the NHS LCD Pilot Programme)		

How to adjust diabetes medications

Depends how many medications the patient is taking

- 1-2 glucose-lowering agents: should stop these agents on the first day of TDR
- ≥ 3 agents should stay on metformin only (or, if not taking metformin stay on an oral agent which is safe with TDR, e.g. DPP4 inhibitor or pioglitazone) and stop the remaining glucose-lowering agents on the first day of TDR.

The medication changes (including the absence of changes) must be specified in writing to the patient and PTR provider at time of referral

DAY 1 TDR Deprescribing
What would you do…

1. Anja is on **metformin**
2. Baljit is on **metformin and gliclazide**
3. Clare is on **metformin, empagliflozin, and liraglutide.**
4. David is on **metformin, sulfonylurea and DPP4 inhibitor**
5. Franz is on **sulfonylurea, SGLT2 inhibitor, and DPP4 inhibitor**

Restarting medications

If Momenta flags that blood glucose is above 15 or HbA1c at 6 or 12 months has risen:

- Metformin first line and is also safe in TDR
- Pioglitazone or DPP4 inhibitors are also safe in TDR

Sulfonylureas, meglitinides or SGLT2 inhibitors **MUST NOT** be used during TDR for safety reasons

If insulin initiation is deemed clinically necessary at any stage they MUST stop the programme

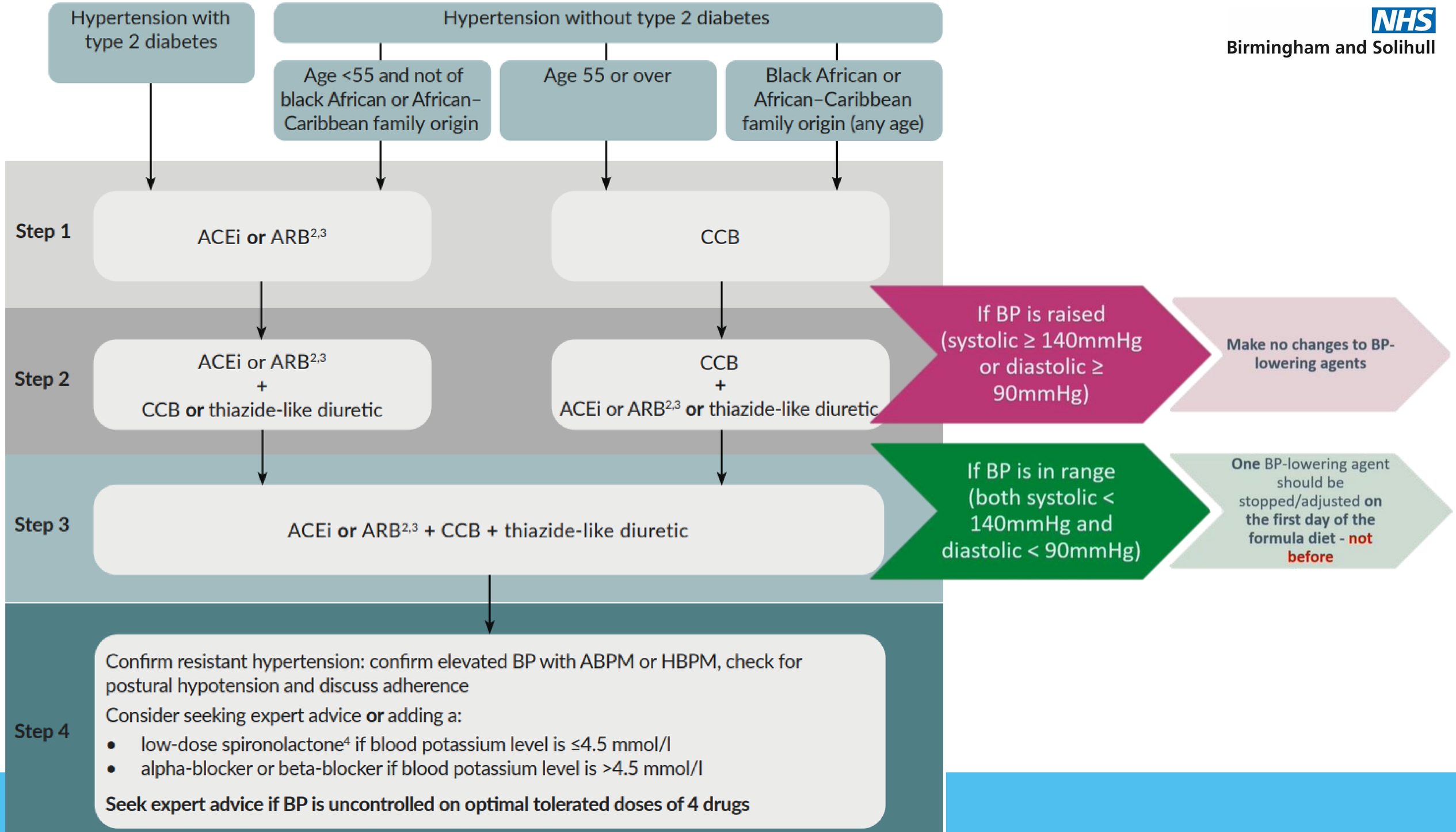
Blood pressure medications

Agents being used specifically and solely for managing blood pressure, in a particular patient, are the **priority** for adjustment

Stop the agent would have been added last according to current NICE guidance [at present, this is NICE guideline NG136 (2019)

Medications which affect blood pressure, but all are being used for other indications e.g. Propranolol, Doxazosin, Bisoprolol.

Use clinical judgement and shared decision making and take into account the blood pressure reading. Cautiously reduce the dose of this agent rather than stopping it.


Hypertension with type 2 diabetes
Hypertension without type 2 diabetes
Age <55 and not of black African or African–Caribbean family origin
Age 55 or over
Black African or African–Caribbean family origin (any age)
Step 1
ACEi or ARB[2,3]
CCB
Step 2
ACEi or ARB[2,3] + CCB or thiazide-like diuretic
CCB + ACEi or ARB[2,3] or thiazide-like diuretic
If BP is raised (systolic ≥ 140mmHg or diastolic ≥ 90mmHg)
Make no changes to BP-lowering agents
Step 3
ACEi or ARB[2,3] + CCB + thiazide-like diuretic
If BP is in range (both systolic < 140mmHg and diastolic < 90mmHg)
One BP-lowering agent should be stopped/adjusted on the first day of the formula diet - not before
Step 4
Confirm resistant hypertension: confirm elevated BP with ABPM or HBPM, check for postural hypotension and discuss adherence
Consider seeking expert advice or adding a:
• low-dose spironolactone[4] if blood potassium level is ≤4.5 mmol/l
• alpha-blocker or beta-blocker if blood potassium level is >4.5 mmol/l
Seek expert advice if BP is uncontrolled on optimal tolerated doses of 4 drugs

‘other’ medications

It is not possible to provide an exhaustive list of all medications which may need adjustment due to weight / dietary changes

Commonly used oral medicines which **may** require adjustment include:

- Warfarin
- Non-vitamin K antagonist oral anticoagulants (NOACs)
- Digoxin
- Phenytoin
- Ciclosporin
- Antifungals – voriconazole
- Long-term antibiotic therapy (e.g. isoniazid)

Patient monitoring

A key safety mechanism in the NHS Path to remission is the regular monitoring of participants' blood glucose and blood pressure (in people prescribed agents affecting blood pressure at time of referral) to detect:

- Clinically significant hyperglycaemia
- Clinically significant high or low blood pressure

If the programme is delivered remotely, participants will be supplied with equipment and training to undertake self-monitoring by the Path to remission Service Provider, with participants communicating readings directly to the Provider

Any readings requiring action, including adjustment of medications, will be communicated to the GP practice with appropriate urgency

Medication Adjustment Form (MAF)

Common issues with MAF

1) **Patients not receiving a copy of MAF**

2) **Where no medications require adjusting you MUST complete the medication's adjustment table**

3) **List all current medications: Where the patient takes medicines that can lower BP this will be identified and a BP monitor can be delivered to the patient.**

Final Points

Make sure you know ALL the medicines the patient is taking – Check Acute medications as well as Repeats/variable repeats

Ask yourself ‘‘if someone lost weight or had a major dietary change, is the dose of this medicine likely to need adjustment?’
If in doubt, discuss with a pharmacist colleague

It is the responsibility of the referrer to make sure that processes are in place for any applicable medications to be adjusted

If this cannot be done safely then the patient should not be referred to the Path to remission programme