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Case study 2

The treatment of a newly diagnosed diabetic patient

This report is a summary of a webinar presentation by Dr Lombard, 22 September 2020.

How would you treat a newly diagnosed diabetic patient?

Case 2 – Mr DvW, newly diagnosed with type 2 diabetes mellitus (T2DM)

- 45-years-old, diagnosed three months ago by GP
- Random glucose: 16.2 mmol/l, HbA_{1c}: 7.8%
- Referred for assessment and opinion
- Dyslipidaemia and hypertension, central obesity, BMI: 35 kg/m^2.

Dr Lombard's clinical approach

This patient requires intensive lifestyle modification because he can still reverse his T2DM in the first five years after diagnosis. But once again I'm a bit sceptical; in my 18 years' experience in endocrine practice, I've found that very few patients are motivated enough to achieve intensive lifestyle modification over the long term. I usually try to motivate these patients very strongly, as the years of potential life lost are in excess of 15. I discuss this with them: "What do you plan to do when you retire? What are your dreams? Diabetes can potentially

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take 15 years of those expected retirement years that you wish for….” Suddenly they seem significantly more motivated. Optimal cardiovascular risk factor control is critical to minimise that expected 15-year life loss.

Extended-release metformin is the gold-standard antidiabetic treatment to initiate, preferably at a low dose. For the patient who has not previously been on chronic medication, initiating a combination of numerous medicines (metformin, statin, antihypertensive) may result in the patient initially not feeling very well. So, as in a marathon, we initiate the extended-release metformin at a low dose and slowly up-titrate to 2 g per day, if tolerated, as this dose gives the patient the maximum benefit. I often consider a dipeptidyl peptidase-4 (DPP-4) inhibitor as an add-on to the metformin therapy, the underlying reasoning being that you must hit hard early, when the patient still has beta-cell reserves. Try to get the patient to a normal HbA_{1c}, preferably even < 6%, and that will reset the beta cells. You save beta cells and help the patient achieve the best outcome.

Management of T2DM – focus on metformin

South African guidelines

The 2017 Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines are outlined in Figure 6. It is important to note that these apply to all T2DM patients who are not pregnant, without metabolic compensation (which is an indication for insulin), and who do not have cardiovascular disease (Figure 1).[1] The SEMDSA guidelines also emphasise that intensive lifestyle intervention is required throughout the management of diabetes. Metformin is recommended as the standard therapy across all categories, discontinued only if contraindications arise or occasional serious side effects occur. Side effects are mostly dose-related and can be addressed by reducing the dose and maybe starting with a lower dose.

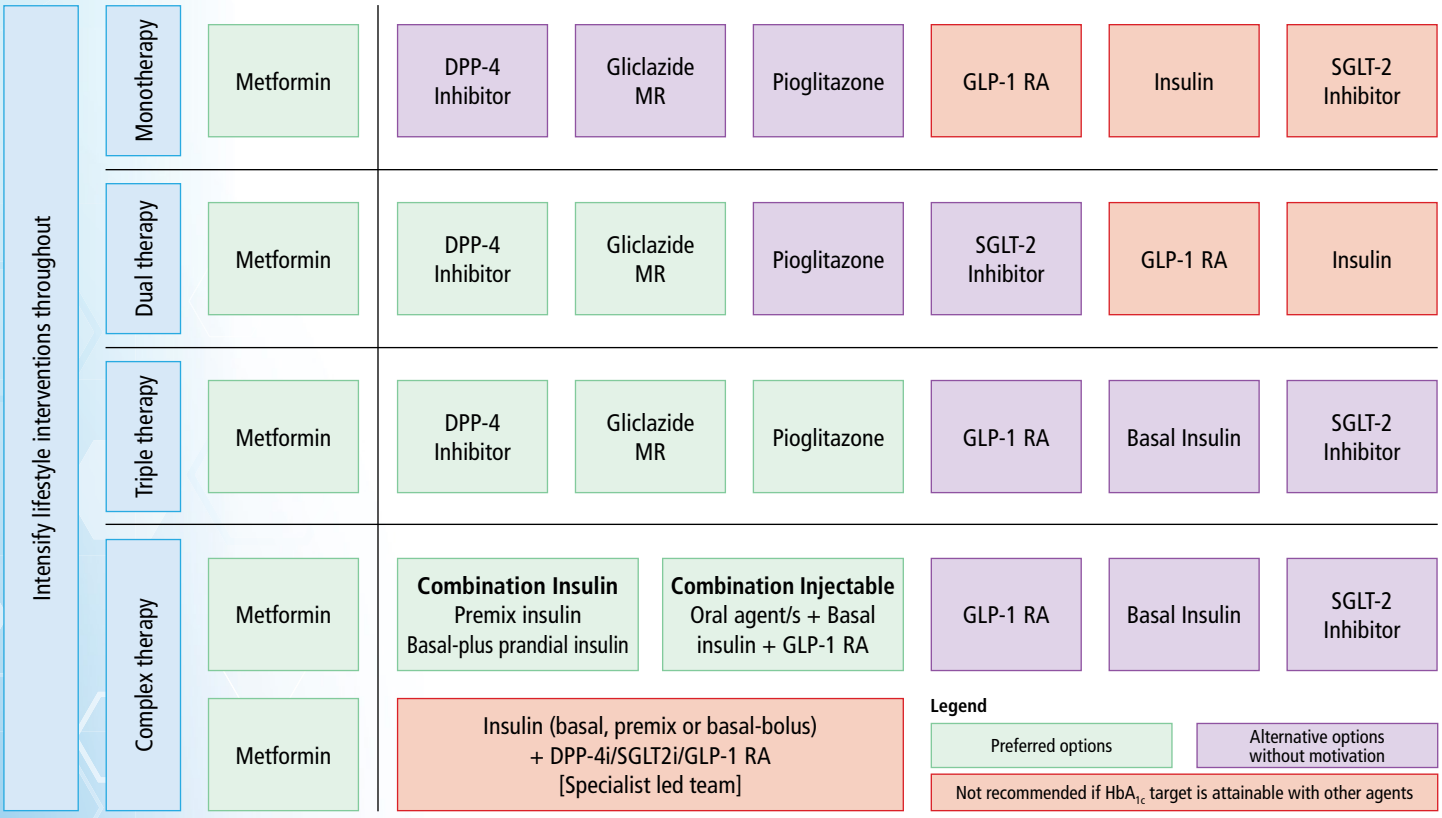

Figure 1. 2017 SEMDSA algorithm for the management of T2DM in non-pregnant adults without metabolic decompensation or cardiovascular disease[1]

The 2018 ADA/EASD consensus guidelines

The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus statement, updated in 2019, makes the following standard treatment recommendation: metformin plus lifestyle management; weight loss is preferable, with physical exercise being the second arm of lifestyle modification. In cases of T2DM with established atherosclerotic cardiovascular disease or chronic kidney disease, different therapeutic approaches are then followed.

It is important to keep in mind that the UKPDS showed that for every 1% reduction in HbA_{1c}, there is a 21% reduction in diabetic deaths, a 14% reduction in fatal and non-fatal myocardial infarction (MI), an almost 40% reduction in microvascular complications and a 43% reduction in the risk of amputation.[2] These impressive results should strengthen our efforts to lower HbA_{1c} in our patients (Figure 2).[2]

Sometimes, as healthcare professionals, we are not convincing enough about the medication we prescribe. It is very important when we prescribe something that we convince the patient of the efficacy of the medication, show that we are confident in applying this treatment, and make them aware that these steps will prolong their life

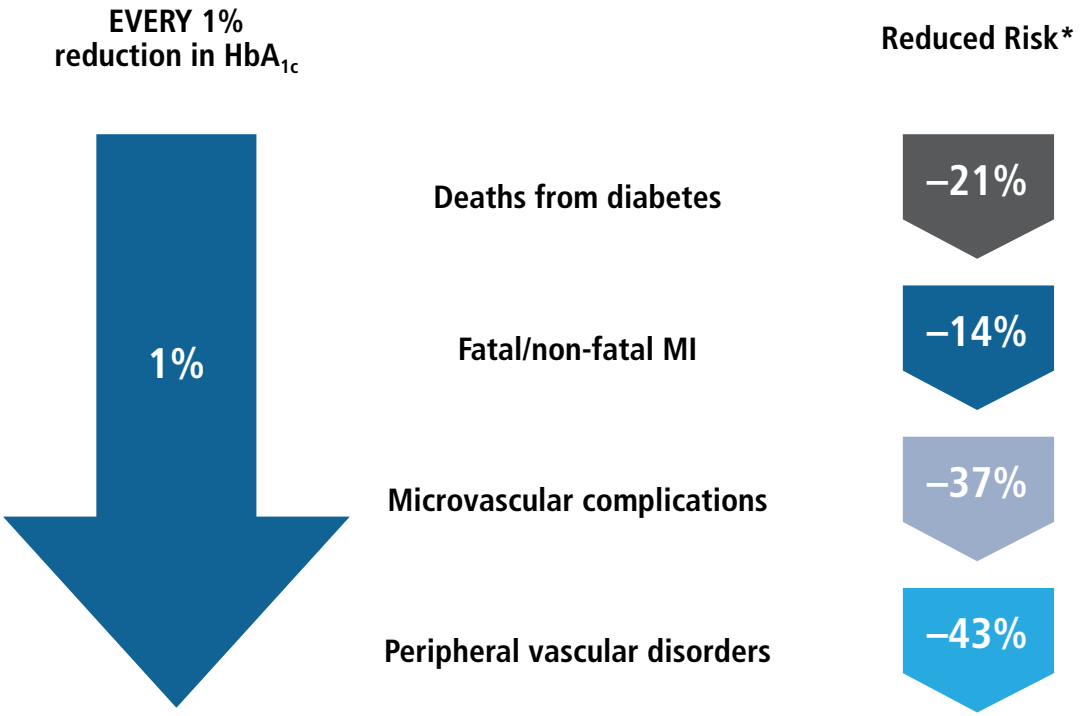

Figure 2. UKPDS showed the importance of glycaemic control[2]

Adherence is fundamental to improved outcomes

It is very important to stress the need to achieve adherence, as it has been well documented that poorer adherence to medication increases mortality. Patients need to know and understand that many of the medications prescribed for diabetes are lifesaving.

Among the factors that influence adherence is that many different medications may be necessary, often to be taken at different times of day. Also, patients may be required to use injectables and may skip their injections because they don't like the process. Some patients, when they experience weight gain, may blame a certain medication and then stop taking it. Certain medications cause hypoglycaemia and fear of this may lead to the patient choosing to stop the therapy. Similarly, they may stop if they think the medication is not showing appropriate efficacy. Other barriers to adherence include affordability and whether there are co-payments, as well as insufficient knowledge of why taking the medicine is so important. Sometimes, as healthcare professionals, we are not convincing enough about the medication we prescribe. It is very important when we prescribe something that we convince the patient of the efficacy of the medication, show that we are confident in applying this treatment, and make them aware that these steps will prolong their life.

Metformin XR has a convenient dosing regimen

Data from extended-release metformin studies show increasing efficacy as the dose is escalated (Figure 3),[3] targeting at least 1.5 g daily but preferably 2.0 g daily as the ideal dose, usually taken in the evening. All diabetes drugs demonstrate better efficacy if initiated at a higher HbA_{1c} baseline and this is also true for metformin. So, if you initiate metformin at HbA_{1c} 9%, for example, you can easily achieve a reduction of 1.5% from baseline. However, if you initiate metformin at 8%, the HbA_{1c} reduction will be less substantial. Metformin is actually quite a potent drug, very closely comparable to the sulphonylureas, and is much more potent than DPP-4 inhibitors and sodium-glucose co-transporter-2 (SGLT-2) inhibitors.

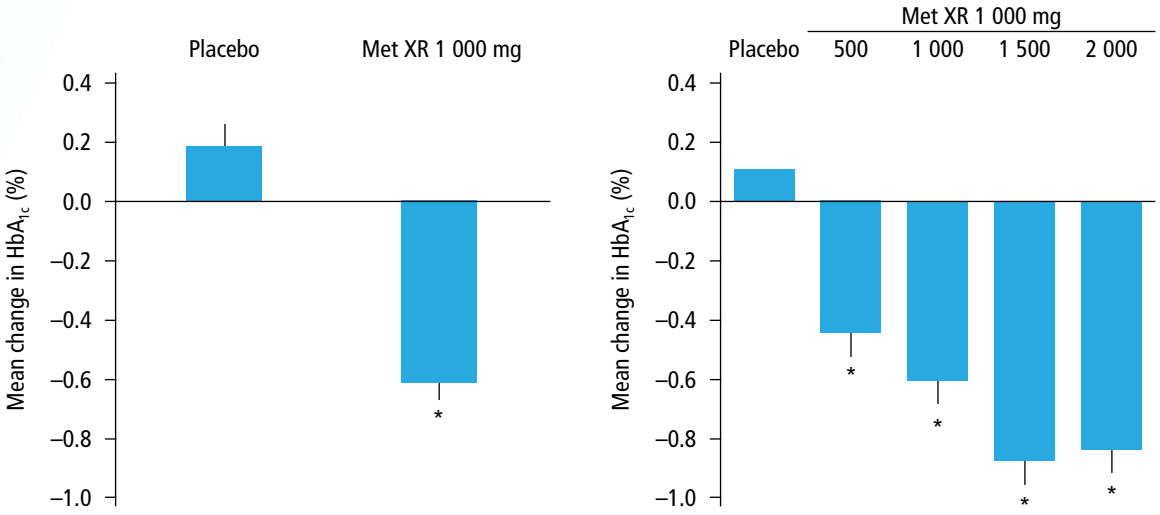

Figure 3. Extended-release metformin has a convenient dosing regimen[3]

You occasionally see people who are intolerant of extended-release metformin, but this is a lot less common than with normal metformin

Metformin XR has improved tolerability

Extended-release metformin was developed to reduce the gastrointestinal side effects that lead to either complete intolerance or a dose-limiting intolerance. Figure 4 illustrates the increased tolerability of the extended-release metformin formulation.[4] You occasionally see people who are intolerant of extended-release metformin, but this is a lot less common than with normal metformin.

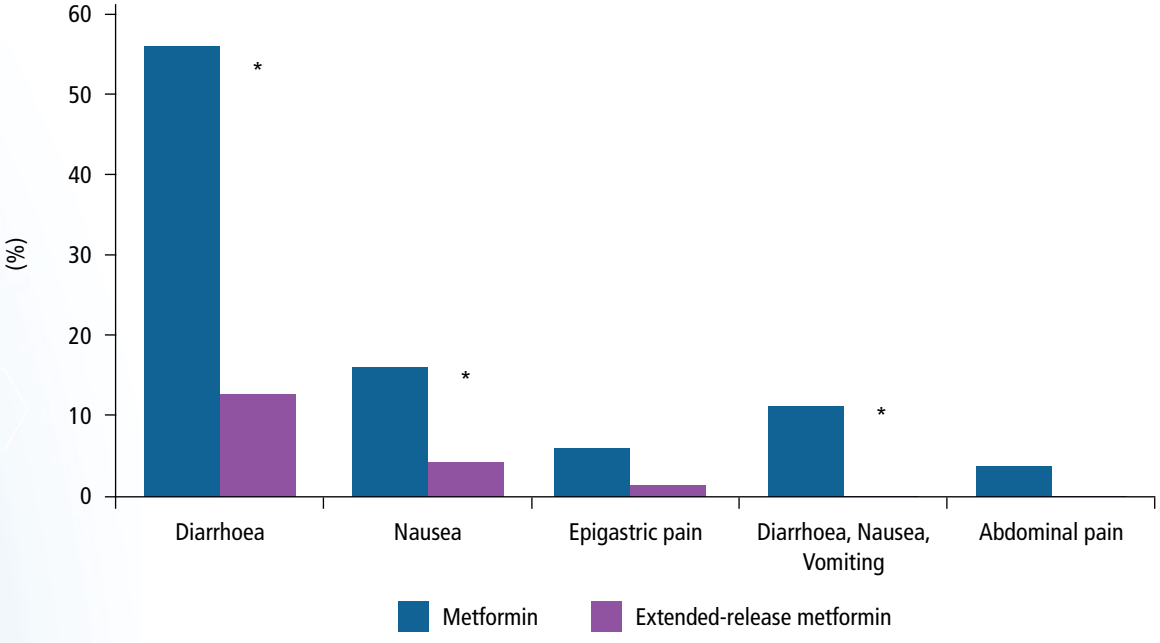

Figure 4. Incidence of gastrointestinal side effects before and after switchover to extended-release metformin in patients completing the 6-month study[4]

The role of cardiovascular outcome trials in diabetes

The United States' Food and Drug Administration has, in the last decade, made cardiovascular outcome trials (CVOTs) compulsory for newer antidiabetic agents. These CVOTs have shown that the DPP-4 inhibitors as a class show no cardiovascular benefit, although it is only saxagliptin that showed an increased risk of hospitalisation for heart failure. The glucagon-like peptide-1 receptor agonists (GLP-1 RAs), however, have shown significant cardiovascular benefit in many studies, and cardiovascular benefit is also observed with SGLT-2 inhibitors, especially reduction in hospitalisation for heart failure.

Metformin has cardiovascular benefits

How does metformin compare to other, often fairly expensive, antidiabetic medications? The UKPDS demonstrated a statistically significant reduction in all diabetic-related endpoints, with a good p-value, when using metformin therapy. This benefit was maintained in the extension trial.[4] Diabetes-related deaths and all-cause deaths were also reduced in the initial study and maintained throughout the extension. MI was reduced and maintained after 20 years. Stroke and peripheral vascular disease were also reduced with metformin therapy, but not statistically significantly for either. A negative factor is that there was no good evidence for a reduction in microvascular endpoints in the UKPDS (Figure 5).[4,5]

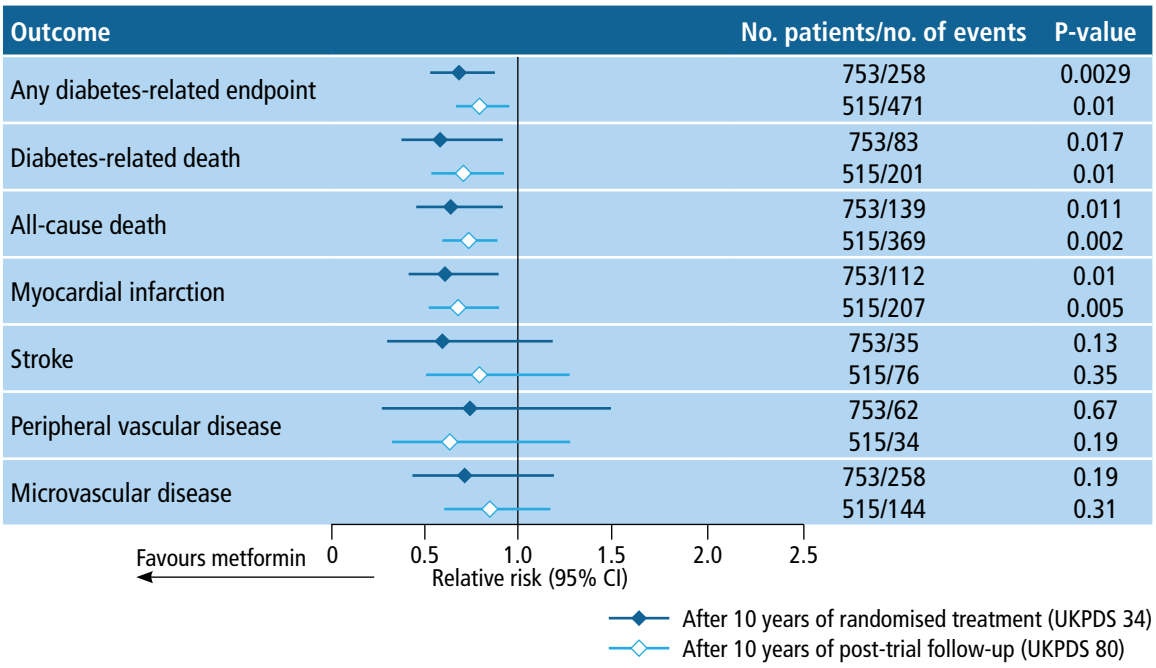

Figure 5. Cardiovascular benefits of metformin[5]

Treating the diabetic patient with kidney disease

An important aspect of metformin therapy is to introduce dose adjustments when kidney disease is present. Metformin can be used safely in patients with an estimated glomerular filtration rate (eGFR) > 45 ml/min/1.73 m^2. If eGFR < 45 ml/min/1.73 m^2, start reducing the dose to 1 g/day. Metformin is contraindicated at < 30 ml/min/1.73 m^2 and should not be initiated at or close to that level. With regard to SGLT-2 inhibitors, there are no dapagliflozin studies in patients with eGFR < 60 ml/min/1.73 m^2 and that agent should therefore not be used in these patients. Empagliflozin, however, can be used with eGFR > 30 ml/min/1.73 m^2. These medications also have very good kidney-protection data.

General practitioners should be careful when introducing these medications at a low eGFR, and rather refer to a nephrologist for specialist opinion. This is also because a drop in eGFR occurs when these agents are initiated and these patients need to be followed carefully. The GLP-1 RA, exenatide, is contraindicated at low eGFRs. Also, liraglutide should not be used with eGFR

< 30 ml/min/1.73 m^2. A recent trial indicated dulaglutide can be used with eGFR > 15 ml/min/1.73 m^2. The only sulphonylurea that can be used in advanced kidney disease is gliclazide MR, but be careful as it can cause hypoglycaemia. I would not use glibenclamide at all, and I would also be careful about using glimepiride in patients with decreasing kidney function, given the risk of hypoglycaemia and accumulation of the dose (Figure 6).[6]

Metformin		**eGFR ≥60ml/min** Standard dosing Monitor eGFR annually	**45-60 ml/min** Standard dosing Monitor eGFR 3 to 6 monthly	**30-45 ml/min** Maximum: 1 000 mg/day Monitor: eGFR 3 to 6 monthly	**< 30 ml/min** Metformin is contraindicated
SGLT2i	Dapagliflozin	Standard dosing	Contraindicated	Contraindicated	Contraindicated
	Empagliflozin	Standard dosing	Allowed	Allowed but be careful	Contraindicated
DPP4i		**eGFR**	**Saxagliptin**	**Sitaliptin**	**Vildagliptin**
		≥ 50 ml/min	5 mg daily	100 mg daily	50 mg twice a day
		30-50 ml/min	2.5 mg daily	50 mg daily	50 mg daily
		< 30 ml/min	2.5 mg daily	25 mg daily	50 mg daily
GLP-1 RA		**eGFR**	**Exenitide**	**Liraglutide**	
		≥ 30 ml/min	1st month - 5 ug BD 10 ug BD thereafter	Initiate at 0.6 mg daily and titrate to a maximum of 1.8 mg daily	
		< 35 ml/min	Contraindicated	Don't use < 30 ml/min	
SU (Gliclazide)		Gliclazide modified-release can be used at all stages of chronic kidney disease using standard dosing. Patients with CKD stage 3 or worse should be monitored by a specialist.			

Figure 6. Dosing considerations in kidney disease[6]

Key learnings

- Slow-release metformin has a low side effect profile
- Once-daily dosing of extended-release metformin improves adherence
- Extended-release metformin can be used in the prediabetic phase.

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Disclaimer: *Dr Landi Lombard*
I received an honorarium for this talk and I serve on several advisory boards, including in the past for Merck.

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