The De Fronzo Treatment Algorithm for the Management of Type 2 Diabetes

This alternative algorithm is compatible with the ADA/EASD and NICE guidelines, but focuses on agents that both address the underlying pathophysiological abnormalities and are capable of delivering treatment targets[1, 2, 3] The evidence cited in the footnotes below suggests that this approach can be highly effective in rapidly achieving the designated blood glucose treatment target and maintaining that level of control.

Triple therapy

EMPAGLIFLOZIN

PLUS

METFORMIN or PIOGLITAZONE

PLUS

DPP4i or GLP-1RA

Rationale

Ryder RE, Defronzo RA. Diabetes medications with cardiovascular protection in the wake of EMPA-REG OUTCOME: the optimal combination may be metformin, pioglitazone and empagliflozin. *Br J Diabetes Vasc Dis* 2015;**15**:151-154

DeFronzo RA, Eldor R, Abdul-Ghani M. Pathophysiologic approach to therapy in patients with newly diagnosed type 2 diabetes. Diabetes Care 2013;36(Suppl. 2): S127–S138), supported by some of the leading diabetologists in the USA (Phillips LS, Ratner RE, Buse JB, Kahn SE. We can change the natural history of type 2 diabetes. *Diabetes Care* 2014;**37**:2668–2676

An exploratory study showed that combination therapy with metformin/pioglitazone/exenatide in patients with newly diagnosed T2DM was more effective and resulted in fewer hypoglycaemic events than sequential add-on therapy with metformin, sulfonylurea and then basal insulin

Abdul-Ghani, M. A., Puckett, C., Triplitt, C., Maggs, D., Adams, J., Cersosimo, E. and DeFronzo, R. A. (2015), Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial. *Diabetes Obes Metab*, **17**: 268–275. doi:10.1111/dom.12417

- Single agents only lower the HbA1c by1-1.5% (11-16 mmol/mol). Thus, when starting HbA1c exceeds 8.0-8.5% (64-69 mmol/mol), more than one agent will be required to achieve the target level.
- Metformin, empagliflozin, pioglitazone and GLP-1 RAs have an additive effect and address underlying pathophysiology.
- Pioglitazone and GLP-1RAS are protective of the β-cell.
- Pioglitazone is a powerful insulin sensitiser. In combination with metformin it improves insulin sensitivity in liver/muscle with a low risk of hypoglycaemia. Combination with a GLP-1RA curbs any weight gain and the natriuretic effect of the GLP-1RA mitigates against the fluid retention. GLP-1 RA lowers hepatic insulin resistance and excessive glucagon secretion. DPP4i's exert similar, but weaker, effects to GLP-1RAs.
- UKPDS and the 10-year follow up study showed that metformin was cardio-protective. Pioglitazone, according to accumulated evidence, reduces cardiovascular death, myocardial infarction and stroke by slowing down or possibly reversing the atherosclerotic process. Empagliflozin reduces cardiovascular death, but not stroke or myocardial infarction. The combination of the three drugs would seem to be advantageous for patients with type 2 diabetes at high cardiovascular risk.
- Metformin, empagliflozin and GLP-1RAs all produce weight loss. DPP4i's are weight neutral.
- The diuretic properties of empagliflozin may mitigate the fluid retention associated with pioglitazone.
- There is very little risk of hypoglycaemia with these drugs, either alone or in combination.