

Where are we in the management of type 2 DM?

Introduction

Diabetes is a multifactorial disease regarding its origin and pathogenesis. The management is addressing the different aspects of its pathophysiology.

Two new concepts of treating DM has emerged during the last decade or so, the incretin-based and the sodium glucose cotransporter inhibitor groups.

The clinical use of the new medication groups has created a revolution that changed our way of dealing with this difficult and annoying disease

Many factors affect the choice of the hypoglycemic agents to be included in the therapeutic plan

- a) Efficacy.
- b) Weight effect
- c) Risk of hypoglycemia
- d) Side effects
- e) Prescribing guidelines
- f) Cost
- g) Cardiovascular and Renal Protection

Efficacy

- a) Oral medications tend to be less effective in lowering HbA1c (< 1% reduction).
- b) Insulin and GLP1 RA reduce HbA1c more, alone or in combination.
- c) Basal insulin and GLP1 RA are similar in reducing HbA1c when used as 1st injectable.
- d) Adding an oral medication looks reasonable when HbA1c is still between 7-8%.
- e) Adding one of the injectable when HbA1c is 8% or above is the most reasonable to a patient on oral medication.
- f) Adding two or more oral medications can bring high HbA1c to goal.

Weight effect

The traditional DM medications

- a) Sulfonylurea
- b) Thiazolidindiones
- c) Insulin Are associated with weight gain
- d) DPP4 Is are weight neutral GLP1 RA and SGLT2 Is are associated with weight loss

Risk of hypoglycemia

- a) Hypoglycemia is a very bad experience for the patient and is now linked to increased morbidity and mortality rate.
- b) It is also related to a higher use of emergency room and hospital services.

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- c) This issue came to the forefront when the DPP4 Is agents became available, as a differentiating feature from SU.
- d) The risk of hypoglycemia with DPP4 inhibitors, GLP1 RA and SGLT2 I is negligible especially when they are not used in combination with insulin or SU
- e) The major differentiating feature between the insulin analogs, especially the newer ultra-long ones, and the human is the lower risk of hypoglycemia
- f) Side Effects
- g) We learn more about safety with a longer clinical experience with a new drug
- h) Unexpected side effects appear with time. Important examples are the increased risk of CHF with some of the DPP4 I, and the increased risk of bone fracture in postmenopausal women with TZD.
- i) The patient should be aware and educated about even uncommon undesirable effect like pancreatitis with incretin-based therapy and amputations with canagliflozin.

Prescribing guidelines

- a) Renal function is one of the most important with DPP4 I and some of the GLP1 RA regarding dose adjustment or contraindications for their use.
- b) SGLT2 Is and metformin have specific renal function guidelines.
- c) Negative or favorable impact on different organs of the body should be considered (heart, kidney, gastrointestinal, liver, bone)

Cost

- a) The cost of prescribing new expensive drugs should be taken into consideration in addition to other factors like insurance type, availability of these drugs in dispensaries and pharmacies of public hospitals.
- b) The ability of the patient to by his medications from his pocket is a last option that can be considered.

Organ Protection

Since 2008 the US FDA requires that all new medications for DM should go through cardiovascular safety serious RCT before approval of use in the American market.¹

The aim of these studies is to demonstrate cardiac safety and the drug is at least not increasing the risk of 3-point MACE (a composite

of major adverse cardiovascular events: recent MI, Stroke, or cardiovascular death).²

Trials of DPP4 I have shown CVD safety for Sitagliptin in TECOS, Saxagliptin in SAVOP-TIMI, and Alogliptin in EXAMINE but saxagliptin and possibly alogliptin increased the risk of hospitalization for CHF.³

Basal insulins, Glargine and Degludec through ORIGIN and DEVOTE trials demonstrated cardiovascular safety but not protection.⁴

ELIXA trial that tested Lixisenatide CVD safety was successful but no protection has been shown.

Clinical trials with new type 2 diabetes medications

SGLT2 inhibitors

September 2015/ EMPA-REG Trial

For the 1st time in the history of type 2 DM management the new drug empagliflozin showed through a RCT of 3 years duration and 7020 participants:

- 1) 14% reduction in the 3-point MACE
- 2) Significant decrease in cardiovascular death and all-cause mortality
- 3) 35% reduction in admission to the hospital for CHF
- 4) No deterioration of renal function in patients with moderate CKD preexisting before the study whether associated with albuminuria or not.

Another SGLT2 I Studies: the CNVAS and CANVAS-R

Patients with either preexisting or high risk for cardiovascular disease were randomized to Canagliflozin or placebo

- 1) 14% reduction in the 3-point MACE
- 2) 40% reduction in a composite renal disease outcome
- 3) 33% decrease in hospitalization due to CHF

Two fold higher amputation rate (toes and feet) in patients who had amputation before or with established PAD.

In a real-world trial that included the three drugs (canagliflozin, dapagliflozin, empagliflozin) compared to other medications used in type 2DM, conducted in 6 countries (UK, Germany, Sweden, Norway, Denmark, US)

- 1) 50% decrease in all-cause mortality
- 2) 40% reduction in incidence of CHF

It is now obvious from the clinical experience with SGLT2 Is that as a class of medication has a significant and rapid positive impact on CHF in addition to their favorable effect on the onset as well as the progression of chronic kidney disease. Beside the decrease in all-cause mortality.

GLP1 receptor agonists

Leader trial

Liraglutide versus placebo in 9340 type 2 DM patients with known cardiovascular disease or having risk factors for CVD.⁵

The study showed 13% decrease in 3-point MACE after 3.8 years of Liraglutide therapy.⁶

The cardiovascular protection was observed after 12-18 months from the beginning of the intervention which indicates probably a regression in the atherosclerotic process.

Another positive finding was a 22% reduction in renal function deterioration as compared with patients on placebo.

Elixa trial

Done with the short-acting GLP1 RA Lixisenatide to demonstrate cardiac safety failed to show cardiac protection but confirmed that the drug is safe.

Sustain 6

Compared Semaglutide to placebo in a RCT of 3297 type 2 DM with established CVD or having high risk for it over 2 years.

The trial showed that Semaglutide is having a potent action in HbA1c and weight reduction.

26% reduction in 3-point MACE outcome, 39% decrease in non-fatal stroke, and 36% in new-onset or deteriorating nephropathy.

76% worsening of preexisting retinopathy most-likely due to the rapid control of DM observed with this potent antidiabetic agent.

The EXSCEL RCT done to demonstrate CVD safety in 14752 type DM patients treated with weekly exenatide failed to show protective effect after 3.2 years follow-up

Conclusion

- 1) Some GLP1 RA has cardiovascular and renal protective effect in type 2 diabetic patients.
- 2) This protective action is delayed as compared to the one observed with SGLT2 Is.
- 3) Absence of protection against congestive heart failure with GLP1 RA available until now.
- 4) Empagliflozin and Canagliflozin have cardiovascular protective effect, renal protective action and favorable effect on hospitalization for heart failure.

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None.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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