INTRODUCTION

The pharmacological armamentarium for the treatment of type 2 diabetes (T2DM) has dramatically expanded over the past 20-30 years. After decades of therapeutic stagnation when glucose-lowering opportunities were only based on biguanides, sulfonylureas, and older insulin formulations, at the turn of the century many new classes of glucose-lowering agents have been made available (1) (Fig. 1). However, this revolution doesn’t seem to be associated with an appreciable increase in the number of T2DM patients attaining, and even more importantly, maintaining good glycemic control. A recent analysis performed on data from 2677 adults from the National Health and Nutrition Examination Survey (NHANES) from 2007 to 2014 showed that percentage of people with diabetes and HbA1c <7.0% slightly declined from 52.2% to 50.9% between the two most recent assessments of the database. Even when attainment of individualized targets based on age and comorbidities were considered, a decline from 69.8% to 63.8% was apparent over the same period of time. Even worse, the percentage with HbA1c >9.0% increased from 12.6% to 15.5% (2). The reason for such partial success despite the development of many new medications to treat diabetes has multiple explanations.

CLINICAL INERTIA IN PEOPLE WITH TYPE 2 DIABETES

Average time for a diabetes consultation for a diabetic outpatient doesn’t take more than 10 min. Too little time is currently spent in diabetes visits for proper interaction with patients and prompt assessment of needs for changing or intensifying treatments. Such a limitation is a main reason for clinical inertia. In a retrospective cohort study based on
81,573 T2DM patients Khunti et al (3) have shown for those with HbA1c <7.0, <7.5, or <8.0% (<53, <58, or <64 mmol/mol), the median time to intensification was 2.9, 1.9, or 1.6 years, respectively, for those taking one OAD and >7.2, >7.2, and >6.9 years for those taking two OADs. Median time to intensification with insulin was >7.1, >6.1, or 6.0 years for those taking one, two, or three OADs. At the time intensification was finally adopted, mean HbA1c was between 8.7 and 9.7%. These observations clearly show that there is major delay in treatment intensification in T2DM patients despite suboptimal glycemic control and that a substantial proportion of subjects remain in poor glycemic control for several years before intensification is considered. The result of such a delayed intensification of glucose-lowering therapy results in non-necessary exposure to hyperglycemia and increased risk of development of diabetic complications.
A recent study by Laiteerapong et al (4) has determined the impact of delayed glycemic control in a cohort study of 34,737 newly diagnosed T2DM subjects. The authors examined associations between HbA1c <6.5% (<48 mmol/mol), 6.5% to <7.0% (48 to <53 mmol/mol), 7.0% to <8.0% (53 to <64 mmol/mol), 8.0% to <9.0% (64 to <75 mmol/mol), or >9.0% (>75 mmol/mol) for various periods of early exposure (0–1, 0–2, 0–3, 0–4, 0–5, 0–6, and 0–7 years) and incident future microvascular, macrovascular and mortality over a mean follow-up of 13 years. Compared with HbA1c <6.5% (<48 mmol/mol) for the 0–1 year early exposure period, HbA1c levels >6.5% (>48 mmol/mol) were associated with increased microvascular and macrovascular events and HbA1c levels >7.0% (>53 mmol/mol) were associated with increased mortality (Fig. 2). These results support the notion that immediate treatment targeting strict and long-lasting glycemic control since the time of diagnosis of diabetes is necessary to prevent long-term risk for diabetic complications and mortality.

**TYPE 2 DIABETES IS A COMPLEX CONDITION**

Past treatment strategies did not help fighting clinical inertia as the stepwise approach, i.e. adding a drug upon failure of previous one(s), can result in significant delay (3). Moreover, the stepwise approach does not take into consideration the complex pathogenesis of T2DM. It took us a long time to appreciate the central role of impaired insulin secretion and insulin resistance (5) in the development of the disease. It took even longer to realize that other mechanisms such as alpha-cell hyperactivity, incretin deficiency/resistance, inappropriate renal glucose reabsorption, and altered brain integration activity can all contribute to disruption of glucose homeostasis and favor development and progression of hyperglycemia (6).

Such a complex pathogenesis implies that effective treatment may require pharmacologic treatments addressing more than a single pathogenetic mechanism. Current guidelines do not yet recommend combination therapy at the time of diabetes diagnosis unless glycemic control at presentation is poor (i.e. HbA1c >9%) (7,8). Nonetheless, most guidelines encourage a proactive approach for glucose lowering management in type 2 diabetes. The ADA/EASD position statement, for instance, recommend metformin monotherapy as initial treatment but request considering adding a second drug if HbA1c target is not achieved after 3-month therapy (7). Similarly, upon implementation of dual therapy, triple therapy has to be considered if target HbA1c is not achieved in the ensuing 3 months. It is readily apparent that a large proportion of T2DM patients would be on a much earlier combination therapy were these recommendations carefully implemented. Though early combination therapy may provide more chances to ensure good glycemic control (9) little guidance is made available to the physician with respect of how to select drugs to be used together. This is not a minor aspect to be considered as, given 9 classes of glucose lowering agents currently available the number of possible permutations is as high as 36 for dual therapy and 84 for triple therapy.

An educated selection of combination therapy should require a more solid scientific approach and more carefully generated clinical data. In the next future it may be possible that omics and more accurate phenotypic characterization of each individual together with sophisticated handling of clinical and personal data (i.e. precision medicine) will guide us in such a difficult decision (10). For the time being, it may suffice to analyze elements that may help a more educated selection of combination therapy, in particular: 1. Pathophysiologic basis of the disease. 2. Complementary mechanisms of action. 3. Efficacy- to-safety ratio, and 4. Extra-glycemic properties of glucose-lowering agents.
To the same token, pioglitazone may be seen as an alternative candidate to metformin in the case greater insulin sensitization of peripheral tissues is deemed necessary (11). Of interest, glitazones may also exert beta-cell protection (22). We have previously shown that rosiglitazone can protect human pancreatic islets from lipotoxicity (23). From a clinical point of view, initial combination of pioglitazone and DPP4i has been proven effective and well tolerated (24).

In summary, glucose-lowering agents can be used and combined on the basis of their pharmacologic target. Recently, Abdul-Ghani et al have expanded and tested this approach (25). Drug-naïve, recently diagnosed T2DM subjects were randomized to triple therapy with metformin/pioglitazone/exenatide or classic stepwise approach with an initial escalating dose of metformin followed by sequential addition of sulfonylurea and glargine insulin to maintain HbA1c levels at <6.5% for 2 years (Fig. 3). T2DM patients started on triple therapy had greater reduction in HbA1c level than those receiving conventional therapy (5.95 vs. 6.50%; p < 0.001) with the advantage of a 7.5-fold lower rate of hypoglycemia and a mean weight loss of 1.2 kg vs 4.1 kg weight gain (p < 0.01) in those receiving conventional therapy. The results of this exploratory study show that a combination therapy aiming at improve beta-cell function (exenatide), increase insulin-mediate glucose utilization (pioglitazone) and suppression of hepatic glucose production (metformin) is more effective that the classic stepwise approach.

**COMPLEMENTARY MECHANISMS OF ACTION**

What discussed above already represent an example of complementary mechanisms of action. By using this approach a greater efficacy and possibly a better durability is expected. However, the complementary mechanisms of action can also contribute to enhance or mitigate undesirable effects of glucose-lowering agents. Treatment with sodium-glucose cotransporter 2 inhibitors (SGLT2i) is associated with increased plasma glucagon levels and a paradoxical increase in endogenous glucose production (26,27). The latter may offset to some extent the glucose-lowering efficacy of these medications so that if the increase in endogenous glucose production is prevented, one could expect a greater efficacy. Metformin, as already said, acts mainly at the level of the liver and pre-clinical studies have shown that metformin can offset the persistence of liver glucose output induced by an SGLT2i (28). In keeping with this mechanistic experiment, clinical trials have shown superiority in glycemic control with the combination of metformin and SGLT2i (29).

Incretins can reduce glucagon secretion after the ingestion of a meal, and such a reduction has been claimed to account for up to 50% of the suppression of hepatic glucose production seen with the administration of exenatide (30). Hansen et al. showed that the use of a DPP4i (saxagliptin) together with metformin and a SGLT2i (dapagliflozin) prevented the increase in post-prandial glucagon levels observed with the use of metformin and dapagliflozin, along with an improvement in post-prandial glucose tolerance.
and sulfonylurea, GLP-1 receptor agonists were associated when added to metformin (36). SGLT2i offered the lowest risk of hypoglycemia and body weight gain of single drugs the network meta-analysis evaluated also the relative risk of body weight and blood pressure (40). Palmer et al in Dapagliflozin was also associated with a durable reduction 0.49- 0.72 of 10-fold lower rate of hypoglycemia. than glipizide (0.19 [95% CI 0.12-0.25] vs. 0.61 [95% CI 0.91-1.56]) (9). Other combination may actually be more neutral (41) and help mitigating side effects. This is the case of SGLT2i add-on to pioglitazone (42) showing increased efficacy along with mitigation of the typical body weight gain of pioglitazone. Moreover, the osmotic diuretic action of SGLT2i can also limit fluid retention and, finally, neither drug are associated with risk of hypoglycemia (43). A recent post-hoc analysis assessing safety of triple oral therapy with metformin/saxagliptin/dapagliflozin versus dual therapy with metformin plus dapagliflozin or saxagliptin found that the incidences of adverse events and serious adverse events were similar (44). Interestingly, urinary tract infections were more common with sequential than with concomitant add-on therapy and genital infections were reported only with sequential add-on of dapagliflozin to saxagliptin plus metformin (44).

A careful assessment of the risk-to-benefit of early combination therapy is key in favoring adherence to the treatment. To this extent, availability of fixed-dose combinations can reduce the number of pills to be administered and therefore contribute to patient’s compliance to therapy (45).

In summary, the multiple potential combinations can result in different risk-to-benefit ratio. This should be seen as a further complication in T2DM management but rather as an opportunity for a more personalized treatment.

### EXTRA-GLYCEMISC PROPERTIES

Though glycemic control remains key in reducing the risk of diabetic complication, some glucose-lowering agents may have ancillary effects that may confer greater protection. A typical example is represented by pioglitazone. After this insulin sensitizer was introduced as a glucose-lowering agent it became soon apparent that it also exerted other actions potentially associated with an anti-atherogenic action (46). In the ProActive trial (47), pioglitazone was

### Table 1. Potential benefit of early combination therapy for the treatment of type 2 diabetes and open question that remained to be addressed

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Pending questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provides a rational approach</td>
<td>How durable?</td>
</tr>
<tr>
<td>Tackles pathogenic complexity</td>
<td>Can improve treatment adherence? Takes advantage of complementary mode of action</td>
</tr>
<tr>
<td>Takes advantage of complementary mode of action</td>
<td>Can reduce clinical inertia?</td>
</tr>
<tr>
<td>Provides balance between efficacy and side effects allowing for individualized therapy</td>
<td>Will preserve beta cell function</td>
</tr>
<tr>
<td>May result in more sustained efficacy with beneficial effect in reducing the risk of long term complications</td>
<td>Will the cost be appropriate?</td>
</tr>
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(31). Consistent with these results, slightly better HbA1c, but significantly higher percentage of patients achieving the HbA1c target <7.0% value have been observed in studies with combinations DPP4i (32,33) or GLP1RA (34,35) and SGLT2i as compared to respective mono-therapies.

In summary, drugs with complementary mechanisms of action can be used to either potentiate the individual glucose-lowering efficacy or to prevent metabolic adjustments that may limit full pharmacological potency.

### EFFICACY-TO-SAFETY RATIO

Results of the meta-analysis conducted by Phung et al. (9) shows that initial combination therapy in drug-naïve T2DM patients is associated with better glycemic control that can be attained with metformin mono-therapy with a incremental HbA1c reduction of 0.43% and a 40% increase in the chances to achieve a target HbA1c level of 7.0%. Further analysis has also evaluated the efficacy of individual drugs when added to metformin. Palmer et al have performed a careful comparative analysis of the efficacy of drugs added to metformin (36). Among T2DM adults, there were no significant differences in the associations between any of 9 available classes of glucose-lowering drugs. Though efficacy is usually evaluated in term of HbA1c reduction, it is also important to appreciate the durability of such an effect. From this point of view, glitazones have been repeatedly reported to be more durable than metformin and in particular of sulfonylureas (37), though careful selection of patient is recommended because of the potential fluid retention, risk of heart failure and pathological bone fractures. DPP4i have been evaluated as add-on therapy to metformin up to 2 years and have been shown generally to be as efficacious as sulfonylureas (38) with one 104-week study reporting modest though significant greater improvement in HbA1c at the end of the study (39). More recently, durability of dapagliflozin as add-on to metformin as compared to glipizide has been assessed up to 4 years (40) to show that dapagliflozin was associated with a significantly lower coefficient of failure than glipizide (0.19 [95% CI 0.12-0.25] vs. 0.61 [95% CI 0.49-0.72] along with 10-fold lower rate of hypoglycemia. Dapagliflozin was also associated with a durable reduction of body weight and blood pressure (40). Palmer et al in the network meta-analysis evaluated also the relative risk of hypoglycemia and body weight gain of single drugs when added to metformin (36). SGLT2i offered the lowest odds of hypoglycemia, while, when added to metformin and sulfonylurea, GLP-1 receptor agonists were associated with the lowest risk of hypoglycemia. Sulfonylureas and pioglitazone were at greater risk of body weight gain while SGLT-2 inhibitors and GLP-1 receptor agonists were associated with less weight gain if not weight loss. These observations are of relevance because, in selecting glucose-lowering agent to be combined, besides efficacy, potential interaction with respect to safety must be considered. For instance, a significant increase in the risk of hypoglycemia was found with combination therapy in comparison to metformin mono-therapy [RR 1.56 (1.08–2.26)], but this effect was not significant when trials of combination of metformin with SUs or glinides were excluded [RR 1.20 (0.91–1.56)] (9). Other combination may actually be more neutral (41) and help mitigating side effects. This is the case of SGLT2i add-on to pioglitazone (42) showing increased efficacy along with mitigation of the typical body weight gain of pioglitazone. Moreover, the osmotic diuretic action of SGLT2i can also limit fluid retention and, finally, neither drug are associated with risk of hypoglycemia (43). A recent post-hoc analysis assessing safety of triple oral therapy with metformin/saxagliptin/dapagliflozin versus dual therapy with metformin plus dapagliflozin or saxagliptin found that the incidences of adverse events and serious adverse events were similar (44). Interestingly, urinary tract infections were more common with sequential than with concomitant add-on therapy and genital infections were reported only with sequential add-on of dapagliflozin to saxagliptin plus metformin (44).
evaluated with respect to cardiovascular protection. Though the primary endpoint (non-fatal myocardial infarction, non-fatal stroke, cardiovascular mortality, and revascularization) did not reach the statistical significance, the pre-defined secondary endpoint (the same as the primary with the exclusion of revascularization) was highly significant (HR 0.84, 0.72-0.98, p=0.027). The IRIS study (48) confirmed such cardiovascular protection lending support to an extra-glycemic effect as the trial was conducted in non-diabetic insulin resistant individuals. In the more recent years cardiovascular protection has been associated with the use of SGLT2i (49,50) and GLP1RAs (51-53). Of note, the mechanisms accounting for such a protection may be different for each of these 3 classes of drugs: mainly anti-atherogenic for pioglitazone, mainly hemodynamic and metabolic for SGLT2i, and with some potential direct effect on cardiac myocyte and vessel for GLP1-RAs (54). If that is the case, this may also open up to more studies to evaluate the potential interaction of the combination of these agents not just in term of potentiation of the glucose-lowering efficacy but also with respect to potency of cardiovascular protection.

Even more pertinent to the discussion of early combination therapy is the appreciation and demonstration of effects that some glucose lowering agents may have for prevention of micro-vascular complications. For instance, DPP4i have been claimed to exert a number of effects that may translate into better preservation of the microcirculation (55). Similarly, GLP1RAs have been shown to exert renal protection (56), an effect that appears to be even more pronounced with SGLT2i (57). Specific studies are currently ongoing to test in a direct manner such potential. If these trials will confirm these properties it is not too difficult to envisage the introduction of these medications in early combination therapy with the goal of providing better and more durable glycemic control while conferring protection from vascular complications.

**CONCLUSION**

Modern treatment of T2DM requires a shift in paradigm with appropriate intensification of therapy from the very first time of diabetes diagnosis. The recognition of the complexity of the pathogenesis of T2DM leads to the appreciation of the importance of attacking the disease from different angles, i.e. simultaneous tackling of multiple mechanisms contributing to hyperglycemia. Ensuring immediate glycemic control and maintaining it as long as possible remains of utmost importance to reduce the risk of complications. As such, combination therapy should be introduced if not at the time of diagnosis at least in a stringent and proactive manner so to avoid undesirable exposure to even mild chronic hyperglycemia and provide early and persistent benefits (Tab. 1). Though this sounds rationale and highly desirable a number of questions remain to be answered (Tab. 1). First of all, we will need a more solid ground to support and guide selection of drugs to be used in combination in a given individual. Also, we will need to determine whether early combination therapy can modify, improve, and preserve critical pathophysiological mechanisms such as beta-cell function with the expectation that this will translate into a more durable glycemic control. We will need to assess to which extent combination therapy could affect patient’s adherence and clinical inertia of health care providers, two main factors contributing to loss of glycemic control over time. Finally, careful cost-effectiveness assessment will be necessary in order to weight the sustainability of a more expensive initial therapy.

In summary, much work remains to be done but some of it is already ongoing. Some of these questions will be addressed by ongoing studies such as GRADE (Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study) (58) and VERIFY (Vildagliptin Efficacy in With metformin For earlyY treatment of type 2 diabetes mellitus) (59). GRADE will compare sulfonylureas, DPP4-inhibitors, GLP1- receptor agonists and basal insulin as add-on to metformin in recently (<5 years) diagnosed T2DM patients to ascertain relative maintenance of metabolic control, adverse effects, effects on CVD risk factors, tolerability, and cost-effectiveness. However, SGLT2i will not be included thus precluding the possibility to explore their potential in early combination therapy. VERIFY will investigate the long-term clinical benefits of early combination of metformin plus vildagliptin (a DPP4-inhibitor) versus sequential use of the same two drugs in T2DM patients with recent diagnosis and mild elevation of HbA1c to compare durability of glycemic control, beta-cell function and insulin sensitivity, time to insulin initiation, and the effect on diabetic complications over a 5-year follow-up.

While we wait for the results of these trials and future ones we must appreciate that type 2 diabetes is a severe condition at any stage of the disease, including early phase even in the presence of mild elevation of plasma glucose levels. For this reason, all potential ways to reduce the burden of the disease must be carefully considered.

**ADDITIONAL INFORMATION**

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