PHARMACOLOGICAL PREVENTION OF TYPE 2 DIABETES

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SUMMARY

Besides lifestyle, various pharmacological treatments have proven their efficacy to prevent type 2 diabetes in high-risk individuals, especially those with impaired glucose tolerance. Major placebo-controlled clinical trials demonstrated favourable effects of various glucose-lowering drugs used for the treatment of type 2 diabetes, especially metformin, acarbose and thiazolidinediones (glitazones), although the distinction between a masking and a true preventing effect is difficult with this type of drugs. Because obesity plays a key-role in the pathophysiology of type 2 diabetes anti-obesity agents may also be considered as valuable adjunct to diet therapy, especially orlistat, and perhaps sibutramine and rimonabant. The effects of lipid-lowering agents, such as statins or fibrates, appear rather modest and still controversial in the prevention of type 2 diabetes. In contrast, robust consistent results were reported with angiotensin converting enzyme inhibitors and angiotensin AT1 receptor blockers, especially in patients with cardiovascular disease including hypertension. In conclusion, besides lifestyle intervention that should remain the mainstay for the prevention of type 2 diabetes, many pharmacological approaches may offer new options to prevent, or at least delay, the development of diabetes in at high risk individuals, and thus to reduce the ongoing epidemics and burden of type 2 diabetes.

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1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is associated with excess morbidity and mortality, and is considered as one of the most costly and burdensome chronic diseases of our time [1-3]. It is a dynamic disease with dual defects, i.e. a progressive insulin secretory defect combined with insulin resistance [4-6], and is intimately linked to the so-called metabolic syndrome and an increased risk of cardiovascular disease [7]. It is well established that the development of T2DM results from an interaction of a subject's genetic makeup and their environment [6]. With the increasing prevalence of obesity, the prevalence of diabetes is reaching epidemic proportions [3,8]. The development of obesity seems to be an important factor portending the development of insulin resistance [9], which in the presence of a genetically determined propensity to beta-cell dysfunction results in alterations in glucose tolerance, leading to impaired glucose tolerance (IGT), impaired fasting glucose (IFG) and overt T2DM [6,10]. Several risk factors have been identified, allowing the screening of so-called high risk individuals [11,12]. On the basis of an expert consensus, the American Diabetes Association recommends clinicians consider screening for T2DM individuals with such risk factors as family history, overweight/obesity, and hypertension [13].

Prevention programmes of T2DM depend on the identification of potentially modifiable risk factors [14]. Recently, a great deal of effort has been made on slowing or even preventing the development of T2DM in high risk subjects [15,16]. In this context, a life-style intervention, typically comprising a combination of diet and exercise, can reduce the risk of progression from IGT to T2DM by up to 58% [17,18]. The precise mechanisms by which lifestyle changes reduce the rate of development of T2DM in these prevention studies have yet to be reported. However, one can anticipate that the resultant weight loss, although rather modest, was associated with improved insulin sensitivity [19]. While lifestyle modifications are clearly beneficial in reducing the risk of developing T2DM, they cannot be implemented in all clinical settings and are not practical for all subjects [20-22]. In addition to lifestyle strategies, various pharmacological approaches have already proven their efficacy in preventing or delaying T2DM [23,24]. Therefore, drug therapy targeting either insulin resistance, or beta-cell function, or both may be considered to prevent T2DM [25]. Primary prevention may be important in the pediatric population because of the rapidly increasing risk in adolescents due to the obesity epidemics, although no long-term clinical trial is available in this population yet [26]. Almost all antihyperglycaemic agents used for the treatment of T2DM [27] have been assessed or are currently evaluated in clinical trials aiming to prevent the development of T2DM in high risk patients : insulin secretagogues (sulfonylureas and glinides), metformin, thiazolidinediones (glitazones), acarbose and even insulin [28,29]. One key question when analyzing the results of these trials is to be able to

distinguish between a true preventing, a delaying or only a masking effect of diabetes by the antihyperglycaemic effect of the drug [30,31]. As obesity plays a crucial role in the pathophysiology of T2DM, anti-obesity agents may be considered for the prevention of diabetes in overweight/obese patients, especially those with abdominal obesity [9]. Various anti-obesity compounds such as orlistat, sibutramine and rimonabant have been or are currently evaluated to prove their efficacy in preventing the development of T2DM [28,29]. Because of the complex pathophysiology of T2DM [5,6,10], other pharmacological strategies have also been considered. On the one hand, lipotoxicity has been shown to promote both insulin resistance and defect in insulin secretion [32]. Therefore, lipid-lowering agents may theoretically be used in an attempt to prevent T2DM, although observational data in clinical trials with statins and fibrates gave rather disappointing results [28,29]. On the other hand, activation of the renin-angiotensin-aldosterone system (RAAS) appears to have deleterious effects on glucose metabolism and numerous trials have analyzed the potential beneficial effects of angiotensin-converting enzyme (ACE) inhibitors or of angiotensin receptor blockers (ARBs), especially in patients with cardiovascular disease [33]. In postmenopausal women, combined therapy with estrogen and progestin has also been shown to be associated with a reduction in the incidence of T2DM, despite a negative effect on cardiovascular risk [34]. A major objective in the future will be to compare the clinical outcomes and cost-effectiveness of all these strategies for managing people at high risk for diabetes, especially pharmacological approaches with intensive lifestyle intervention [35].

The aim of the present review article is to describe and discuss the results of clinical trials demonstrating a preventive effect of various pharmacological compounds in the development of T2DM in at risk individuals. We will successively consider the effects of various glucose-lowering agents, anti-obesity drugs, lipid-lowering agents, and inhibitors of the RAAS, to end up with various agents (estrogens) and new perspectives (anti-inflammatory compounds).

2. PREVENTION BY GLUCOSE-LOWERING AGENTS (Figure 1)

2.1. Metformin

Metformin is now considered as the first-line drug for the treatment of T2DM [36] and appears to exert several metabolic effects that may be favourable in patients with abdominal obesity and IGT [37,38]. Metformin primarily reduces glucose output from the liver, despite no reduction in liver fat [39], and could also increase, although to a rather small extend, glucose uptake in the peripheral tissues in the presence of insulin, thereby reducing demand on the B cell. Interestingly, favourable effects of metformin on body mass index and glucose tolerance have also been observed in obese adolescents with fasting hyperinsulinaemia and a family history of T2DM, a subgroup of individuals who are

known to be at high risk to later develop diabetes [40]. A few old studies investigating biguanides (metformin) found no significant reduction in the incidence of T2DM compared with placebo using intention-to-treat analyses. However, all of these studies had very low diabetes incidence and were likely underpowered [28].

The largest and most methodologically rigorous trial was the Diabetes Prevention Program (DPP) performed in the United States [18]. It randomized 2.155 individuals (age 51 years, BMI 34 kg/m², 45% high-risk minority groups) with IGT to metformin (850 mg b.i.d.) or placebo (another arm assessed the effect of intensive life-style intervention). After a mean follow-up period of 2.8 years, the incidence of new diabetes was 7.8% in the placebo-treated patients versus 4.8% in those treated with metformin (relative risk [RR] = 0.69, 95% confidence interval [CI] 0.57-0.83). To prevent one case of diabetes during a period of three years (number needed to treat or NNT), 14 would have to receive metformin. In post hoc subgroup analyses, the benefits of metformin were primarily observed in young patients (> 60 years) and in obese patients (BMI > 35 kg/m²). In order to avoid a direct metabolic effect of the drug [41], subjects were submitted to a final investigation after a 1-2-week wash-out period. In the 79% of eligible patients who completed this last visit, the incidence of diabetes increased from 25.2 to 30.6% in the metformin group and from 33.4 to 36.7% in the placebo group [42]. When results of the washout period were included in the overall analysis, metformin still significantly decreased diabetes incidence (RR = 0.75, 95% CI 0.62-0.92). However, as pointed out [31], the washout period was rather short (1-2 week only), which could not definitely exclude a partial masking effect [43]. Moreover, because type 2 diabetes is a progressive disease [4,5,10] and because the study was rather short (2.8 years), it remains to demonstrate whether the effect attributed to metformin is really a true preventing effect rather than only a delaying effect [30]. Finally, it should be pointed out that the reduction in the incidence of T2DM with metformin (31 %) was lower than that obtained with intensive lifestyle intervention (58 %) [18].

In the Chinese Diabetes Prevention Study, subjects with mild overweight (BMI : 25 kg/m²; age : 50 years) and IGT were divided into a control group (n = 85) which received conventional education, a metformin group (n = 88 : 250 mg t.i.d.) and an acarbose group (n = 88 : 50 mg t.i.d.) (see below 2.4) [44]. Over a 3-year period, 34.9% in the control group versus 12.4% in the metformin group progressed to diabetes. This represents an impressive risk reduction of 76.8% for metformin, despite the absence of significant weight loss. Unfortunately, the procedure of randomization was not described in the paper.

The Early Diabetes Intervention Trial (EDIT) was a six-year, prospective, randomised, double-blind, placebo-controlled study in subjects thought to be at increased risk of developing

diabetes, and who had two consecutive fasting plasma glucose levels in the range 5.5 to 7.7 mmol/L. The primary aim of this UK trial was to determine whether deterioration in glucose tolerance towards diabetes could be delayed or prevented using a biguanide (metformin, 500 t.i.d.) or an alpha-glucosidase inhibitor (acarbose, 50 t.i.d.) (see below 2.4) [45]. The 2 x 2 factorial design of this study has the potential to reveal a synergistic effect between metformin and acarbose on diabetes prevention. However, the double intervention group is small with just over 160 patients and may be underpowered to find such synergy. Six-year results for both arms have been published only as abstracts and primary analyses showed no significant difference between groups [45]. Of the initial cohort, 31% became diabetic and 14% discontinued follow-up. No differences were seen in RR for diabetes by 6 years with metformin (RR = 0.99; p = 0.94) or combination metformin-acarbose therapy (RR = 1.02; p = 0.91) as compared to placebo. Similarly, non significant differences were observed versus placebo in those patients with IGT at baseline.

More recently, the Indian Diabetes Prevention Programme (IDPP-1) randomized 531 individuals with IGT in four groups, control, lifestyle alone, metformin alone (250 mg b.i.d.) and combined lifestyle plus metformin. This trial confirmed that lifestyle modification and metformin prevent T2DM in Asian Indian subjects with IGT [46]. However, there was no added benefit from combining the two approaches after a median follow-up period of 30 months. Of note the average dose of metformin was only 250 mg twice daily, thus much lower that that used in the US DPP [18]. The 3-year cumulative incidences of diabetes were 55.0% in the control group, 39.3% in the group with lifestyle modification, 40.5 % in the group treated with metformin and 39.5% in the group given lifestyle advice + metformin. Thus, the relative reduction was 26.4% with metformin alone (95% CI 19.1-35.1, p = 0.029), and 28.2 % with combined approach lifestyle plus metformin (95% CI 20.3-37.0, p = 0.022). The NNT to prevent one incident case of diabetes was 6.4 for lifestyle alone, 6.9 for metformin and 6.5 for lifestyle plus metformin. The absence of synergistic effect may be disappointing, especially because the RR reduction of diabetes with lifestyle modification was less in the Indian Diabetes Prevention Programme compared with the 58% reduction in previous trials, especially the US DPP [18]. In this latter trial, part of the metformin effect was attributed to a modest weight loss, which was not observed with metformin in the Indian trial, possibly because of the lower daily metformin dose used.

Thus, most of the trials performed with metformin gave positive results, despite some heterogeneity. As metformin benefits from a long-lasting clinical experience, is generally well-tolerated and is a rather cheap drug, it should be considered not only as the first choice drug for the management of hyperglycaemia in patients with type 2 diabetes [36], but also as a valuable option

for the prevention of type 2 diabetes in high-risk individuals, especially those with IGT [35].

2.2. Sulphonylureas/glinides

While defective insulin secretion has been long considered as a latter event in the natural history of T2DM, recent studies have clearly demonstrated that there is an early defect in B-cell function [47], even in individuals with IGT [48], especially when insulin secretion is evaluated in comparison with insulin resistance [5]. Therefore, the use of insulin secretagogue agents might be considered as a potential alternative to prevent progression to T2DM, even if the risk of hypoglycaemia may be a serious limitation in clinical practice [49]. As reviewed by Alberti [50], the first-generation compound tolbutamide showed positive results in 5 out of 7 intervention trials. However, data interpretation is complicated by the fact that these trials preceded the modern definition of IGT and studied "borderline" or "chemical" or "latent" diabetes. Two old studies examined the effect of tolbutamide therapy (1000-1500 mg/day) on diabetes incidence in patients with IGT or high-normal/elevated fasting glucose levels [51,52]. Neither study reported a statistically significant decrease in the incidence of T2DM compared with control or placebo, although both studies were small (n = 97 and n = 248) and potentially underpowered. These negative results were confirmed in a larger and more recent trial (Fasting Hyperglycemia Study, reported only in an abstract form) showing that sulphonylurea therapy (gliclazide) over six years does not delay progression to diabetes [53]. In this trial, hypoglycaemia was a potentially limiting side effect of sulfonylurea therapy, occurring at a frequency of 3% in non-diabetic patients. Perhaps an ongoing trial should provide more definitive evidence of the potential interest of sulphonylureas. Indeed, the NEPI Antidiabetes Study (NANSY) has recruited almost 2,000 individuals with fasting glucose levels of 5.6-6.0 mmol/l, who will be randomized to glimepiride or placebo and followed for 5-7 years with diabetes as primary endpoint [54].

Because new insulin-secreting agents of the meglitinide family (repaglinide, nateglinide) have a more favourable pharmacokinetic profile that allows to better control postprandial hyperglycaemia while reducing the risk of late hypoglycaemia [55], they represent a possible alternative to sulphonylurea for the prevention of T2DM. No such demonstration is available yet neither with repaglinide nor nateglinide. However, a large trial (NAVIGATOR : "Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research") is currently investigating the effect of nateglinide in high risk subjects [56]. This multinational, randomised, double-blind, placebo-controlled, forced-titration, 2 x 2 factorial design trial assessed the effect of nateglinide (30-60 mg t.i.d.) and valsartan (80-160 mg od) (see below 5.2) on the prevention of diabetes and cardiovascular events in approximately 7500 subjects with IGT and increased risk for a cardiovascular event. The delay or prevention of

progression to diabetes will be evaluated in the core phase of the study (3 years) whereas the prevention of cardiovascular events will be evaluated during an extension phase in the same patients. The efficacy of nateglinide and valsartan will be determined prospectively using validated measures of diagnosis of diabetes, i.e. oral glucose tolerance tests (OGTTs) and/or fasting glucose levels [56].

Thus, the place of insulin secretagogues in the prevention of T2DM is not obvious yet. To this respect data from the NAVIGATOR trial are awaited with interest. If positive, i.e. reduced incidence of new onset diabetes with a good safety profile, this approach will offer a new alternative for the prevention of T2DM in high-risk individuals. New agents capable of stimulating insulin secretion and possibly protecting and even regenerating B-cell as well, such as GLP-1 analogues and DDP-IV inhibitors, offer new exciting perspectives [57]. However, the cost of the new drugs will be higher and there are no clinical trials available (or ongoing) demonstrating their interest in the prevention of T2DM yet.

2.3. Glitazones

TZDs (glitazones) are insulin-sensitizers with glucose-lowering effects, which are increasingly used for the treatment of T2DM [58]. These agents increase insulin sensitivity, both in the peripheral tissues (muscle and fat) and liver (reducing hepatic fat depot), thereby decreasing the glucose load on the B cell [39]. Besides this classical effect, TZDs may exert beneficial cardiovascular effects and protection of B cell, by preserving cell mass and improving insulin secretory function [59,60]. The Troglitazone Prevention of Diabetes (TRIPOD) study reported a marked reduction in the incidence of T2DM from 45% with placebo to 20% with troglitazone (RR = 0.45, 95% CI 0.25-0.83) in 236 overweight Hispanic women with previous gestational diabetes (age 35 years, BMI 30.5 kg/m²) [61]. This effect was observed after a 2.5 year follow up and occurred despite a modest and nonsignificant weight gain of 0.3 kg compared with placebo. However, the nearly 33% attrition rate during follow-up is a major limitation of this study. In addition, troglitazone has been withdrawn from the market because of liver toxicity [62]. The Pioglitazone In Prevention Of Diabetes (PIPOD) study was conducted to evaluate β-cell function, insulin resistance, and the incidence of diabetes during treatment with pioglitazone in Hispanic women with prior gestational diabetes who had completed participation in the TRIPOD study [63]. Women were offered participation in an open study with pioglitazone (30 mg/day, uptitrated to 45 mg/day) treatment for 3 three years and 6 months of postdrug washout. Metabolic investigation includes both oral and intravenous glucose tolerance tests. The similarity of findings between the PIPOD and TRIPOD studies supports a class effect of TZDs to enhance insulin sensitivity, reduce insulin secretory demands, and preserve pancreatic β-cell function, all in association

with a relatively low rate of T2DM. The lowest rate of diabetes occurred in association with the greatest reduction in insulin secretory demands during the first year of treatment. Taken together, findings from these two trials support a role for TZDs to modify the natural history of progression to T2DM in high-risk Hispanic patients. The generalizability to other high-risk groups will require additional studies.

In a small cohort study on 172 patients with IGT and insulin resistance, a significant reduction in diabetes incidence was observed with thiazolidinedione therapy (troglitazone followed by either rosiglitazone 4 mg od or pioglitazone 30 mg od) versus a untreated comparison group after a 3-year follow up (RR = 0.11, 95% CI 0.03-0.36) [64]. It was concluded that progression of insulin resistance and IGT to T2DM appears to be delayed or prevented with early TZD treatment.

In the US Diabetes Prevention Program (DPP), troglitazone (400 mg od) was used initially but was discontinued during the trial for safety reason [18]. During the mean 0.9 year (range 0.5-1.5 years) of troglitazone treatment, the diabetes incidence rate was 3.0 cases/100 person-years, compared to 12.0, 6.7, and 5.1 cases/100 person-years in the placebo, metformin and intensive lifestyle participants (p < 0.001, troglitazone versus placebo and p = 0.02 troglitazone versus metformin) [65]. However, during the three years after troglitazone withdrawal, the diabetes incidence rate was almost identical to that in the placebo group. It was concluded that troglitazone markedly reduces the incidence of diabetes during its limited period of use, but that this action does not persist after drug withdrawal. Whether other thiazolidinedione drugs used for longer periods can safely prevent diabetes remains to be determined.

The DREAM ("Diabetes Reduction Assessment with ramipril and rosiglitazone Medication") randomised clinical trial evaluated the effect of rosiglitazone (8 mg od) versus placebo to prevent T2DM in a large cohort of 5269 individuals with IFG and/or IGT [66]. Rosiglitazone (at a maximal daily dose of 8 mg) for 3 years substantially reduced incident T2DM (RR = 0.39; 95% CI 0.34-0.45; p < 0.0001) and increased the likelihood of regression to normoglycaemia in adults with mild dysglycaemia at baseline (RR = 1.70; 95% CI 1.56-1.86; p < 0.0001) as compared to placebo. However, as for the first report of the DPP on metformin [18], results recently published in the original paper [66] were obtained on treatment with rosiglitazone. In the US DPP, part of the prevention effect of metformin disappeared after a short period of washout of only 1-2 weeks [42]. Thus, the question whether the remarkable effect obtained with rosiglitazone in the DREAM study is a true preventing effect or only a delaying effect or even simply a masking effect remains an open question [67]. Data from a previous troglitazone trial suggested that the benefit of a TZD persists several months after the drug is stopped [61], although this durable effect was not seen in another trial [65]. Therefore, the post-trial washout data of the DREAM study are waiting with great interest [67].

ACT NOW ("Actos Now for Prevention of Diabetes") is a smaller ongoing study (n = 600) assessing the efficacy of pioglitazone compared to placebo on the prevention of T2DM as primary objective in subjects with IGT. The diagnosis is based on 2 OGTTs as recommended [12] and the subjects will be treated for approximately 3 years. The results should be available by year 2008.

Currently available data suggest that glitazones are the most promising drugs for the prevention of T2DM. However, the rather high cost of such pharmacological approach and the possible occurrence of adverse effects (weight gain, fluid retention, congestive heart failure) may limit the use of TZDs in this indication in the future, especially if high dosage (as in the DREAM trial) is recommended [67]. One alternative to increase the efficacy while improving the cost-effectiveness might be to use combination pharmacological therapy such as rosiglitazone plus metformin, in addition to a healthy lifestyle programme, as currently evaluated in the moderately sized "Canadian Normoglycemia Outcomes Evaluation" (CANOE) study in subjects with IGT [68].

2.4. Acarbose

Antidiabetic drugs of the family of α-glucosidase inhibitors comprise three compounds : acarbose, miglitol and voglibose. Their mechanism of action is to retard carbohydrate absorption and reduce postprandial glucose responses by inhibiting α-glucosidase enzymes present on the brush border of the small intestine which hydrolyze di- and oligosaccharides into their component monosaccharides [69]. Of the three α-glucosidase inhibitors, only acarbose has been specifically evaluated in its ability to prevent or delay the progression from IGT to T2DM [70]. Acarbose, although almost not absorbed from the gut, has been reported to reduce insulin resistance, perhaps through lower postprandial plasma glucose concentrations reducing both glucose toxicity and demand on the B cell, and to have the potential of preventing diabetes in patients with IGT.

The STOP-NIDDM trial is an international multicentre, placebo-controlled study on the efficacy of the α-glucosidase inhibitor acarbose in preventing or delaying the development of T2DM in a population with IGT [71]. A total of 1,429 subjects (age 55 years, BMI 31 kg/m²) diagnosed with IGT and having a fasting plasma glucose concentration $\geq$ 5.6 mmol/l were randomised in a double-blind fashion to receive either acarbose (100 mg t.i.d., n = 714) or placebo (n = 715) for a predictive median follow-up period of 3.9 years. The primary outcome is the development of T2DM diagnosed using a 75-g OGTT. The final analysis of the data regarding primary endpoint showed that 221 (32%) patients randomised to acarbose versus 285 (42%) randomised to placebo developed diabetes (RR = 0.75; 95% CI 0.63-0.90; p = 0.0015). Despite the small weight loss in the acarbose group probably contributed to delaying onset of diabetes, acarbose was still effective after adjustment for weight loss (p = 0.0063).

The results suggest that 11 patients with IGT would need to be treated for 3.3 years to prevent one event of development of diabetes. They also suggest that acarbose effectively reduced risk of developing T2DM irrespective of age, sex, and BMI. If the diagnosis of diabetes was based on 2 OGTT as recommended by the Expert Committee of the American Diabetes Association [12], acarbose treatment resulted in a 36.4% reduction in the incidence of diabetes (p = 0.0003). Furthermore, acarbose significantly increased reversion of IGT to normal glucose tolerance (p < 0.0001). At the end of the study, treatment with placebo for 3 months was associated with an increase in conversion of IGT to diabetes, an observation which again suggests that long-term treatment may be mandatory to prevent diabetes in such at risk patients. It is noteworthy that almost a quarter of patients discontinued early, of whom 48% discontinued during the first year, mostly because of gastrointestinal side-effects. Although the molecular mechanisms still need investigation, it was concluded that acarbose could be used, either as an alternative or in addition to changes in lifestyle, to delay development of T2DM in patients with IGT, especially since the drug has no toxic effects. These conclusions were challenged in a "for debate" paper suggesting that the validity of the results of the STOP-NIDDM trial is seriously flawed, because of selection bias, inadequate blinding, and bias in data analysis and reporting [72]. However, the authors confirmed that the trial results are scientifically sound and credible. The investigators stand strongly behind these results demonstrating that acarbose treatment is associated with a delay in the development of T2DM (as well as hypertension and cardiovascular complications) in a high-risk population with IGT [73].

In the Chinese Diabetes Prevention Study (DPS), subjects with mild overweight (BMI : 25 kg/m²) and IGT were divided into a control group (n = 85) which received conventional education, a metformin group (n = 88) (see above) and an acarbose group (n = 88) [44]. Over a 3-year period, 34.9% in the control group versus 6.0% in the acarbose group progressed to diabetes. This represents an impressive risk reduction of 87.8% for acarbose. However, these remarkable results were only partially confirmed in a UK trial, the Early Diabetes Intervention Trial (EDIT) [45]. Indeed, primary analyses showed no significant difference in relative risk for T2DM between the control group and the acarbose group after a mean 6-year follow-up (RR = 1.04; p = 0.81). However, in those patients with IGT at baseline, RR of conversion to T2DM was reduced significantly with acarbose (RR = 0.66; p = 0.046) [45]. Even if the number of patients in the treatment group was rather small and might be underpowered to show a significant difference, it was not smaller, but rather slightly higher, as compared to the Chinese DPS [44]. A already mentioned, similar discrepancy between the two trials was observed as far as the effect of metformin on diabetes prevention is concerned. The reasons for such discrepancies are not clear,

but may result from the different designs of the two studies, i.e. a randomised controlled trial in EDIT versus a cohort study in the Chinese DPS.

Thus, acarbose, because of its absence of toxicity and its efficacy to prevent T2DM in individuals with IGT in the STOP-NIDDM trial, appears to be a valuable alternative, although not all clinical trials provided clear-cut results. In addition, the cost of the drug, although considered as acceptable when considering the prevention of both diabetes and cardiovascular events [74], and its rather poor gastrointestinal tolerance may represent limitations to use acarbose only for prevention , so that the drug should probably considered only for high-risk individuals.

2.5. Insulin

The ORIGIN study is an international randomized placebo-controlled trial examining the efficacy of glargine insulin (and/or omega 3 in a 2x2 factorial design) in decreasing the risk of cardiovascular events in 12.500 subjects followed for 3.5 years [75]. As a secondary objective, investigators will look at the effect of glargine (and/or omega 3) on the development of T2DM whose diagnosis will be based on OGTT (however, only 19% of the population have IFG and/or IGT at baseline). The results should be available in 2009.

3. PREVENTION BY ANTI-OBESITY AGENTS (Figure 2)

Obesity is strongly associated with T2DM [9,19]. Minor long-term changes in body weight have beneficial effects on insulin sensitivity and beta-cell function in obese subjects [76], which may retard or prevent the progression to T2DM in at risk individuals. Weight loss strategies using dietary, physical activity, or behavioural interventions produced significant improvements in weight among persons with prediabetes and a significant decrease in T2DM incidence [77]. A recent posthoc analysis of the Diabetes Prevention Program revealed that for every kilogram of weight loss, there was a 16 % reduction in risk of T2DM, adjusted for changes in diet and physical activity, and concluded that interventions to reduce diabetes risk should primarily target weight reduction [78]. However, the rate of responders is rather low, the degree of weight loss is generally disappointing and the long-term weight maintenance is questionable with life-style changes. Therefore, various anti-obesity drugs have been developed in order to improve these outcomes [79,80].

3.1. Orlistat

Orlistat is a gastric and pancreatic lipase inhibitor that blocks the absorption of about one third of the fat contained in a meal and thus promotes faecal excretion of undigested fat [81]. In a meta-

analysis summarizing the results of 29 randomized placebo-controlled studies of orlistat (usual dosage of 120 mg t.i.d.), the pooled random-effects estimate of the mean weight loss for orlistat-treated patients compared with placebo recipients was 2.89 kg (95% CI, 2.27 to 3.51 kg) after 12 months [80]. The placebo-subtracted weight reduction induced by orlistat was even less impressive in adults with type 2 diabetes (2.0 kg; CI 1.3-2.8) at 12 to 57 weeks follow-up [82]. Despite this modest weight loss, a significant reduction in HbA1c levels was consistently reported [82]. This suggests that orlistat may enhance insulin sensitivity [83,84], although controversial results have been reported in non-diabetic individuals [85]. A pooled analysis of three 2-year randomised clinical trials enrolling 642 obese patients reported a non-significant reduction in the incidence of T2DM from 2.0 to 0.6% with orlistat therapy (RR = 0.25, 95% CI 0.05-1.2) [86]. The confidence intervals were wide, reflecting the low absolute incidence of diabetes within these trials, and attrition rates averaged > 30%. Nevertheless, these observations lead to the concept that orlistat may prevent T2DM in at risk obese patients [87] and lead to the initiation of the XENDOS trial.

XENDOS ("XENical in the Prevention of Diabetes in Obese Subjects") is the most important RCT performed with orlistat until now, as far as the number of subjects (mean age 43 years, BMI 37.4 kg/m²) enrolled (n =3277) and the duration of the trial (4 years) are concerned [88]. It demonstrates that the beneficial effects of orlistat on body weight persisted up to 4 years (- 6.9 kg with orlistat versus – 4.1 kg with placebo; p < 0.001), although the difference between orlistat and placebo group tended to attenuate over time. The most striking finding of XENDOS is that such a modest difference in weight reduction (mean of 2.8 kg) was sufficient to significantly reduce the cumulative incidence of T2DM (6.2% with orlistat versus 9.0% with placebo; RR = 0.63, 95% CI 0.46-0.86; p = 0.0032). The annual incidence of T2DM in XENDOS was 4-5 times lower than in previously mentioned trials, mainly because only 21% of enrolled subjects had IGT. The reduction in the incidence of T2DM was especially remarkable in those obese patients with IGT at baseline, with a reduction of conversion to T2DM after 4 years decreasing from 28.8% in the placebo group to 18.8% in the orlistat group (p < 0.005) and a NNT to avoid one event of 11 only. However, the attrition rate was 57%, partly due to a higher incidence of gastrointestinal side effects with orlistat. XENDOS is the first study demonstrating that an antiobesity agent, like orlistat, is able to reduce the progression to T2DM in obese subjects as compared with lifestyle changes alone.

3.2. Sibutramine

Sibutramine is a combined norepinephrine and serotonin reuptake inhibitor [89]. At a daily dosage of 10-20 mg, it is associated with increased satiation and a resulting reduction in food intake

(although some thermogenic effects may exist as well) [89]. Weight changes were associated with various favourable metabolic effects [90]. A meta-analysis included 44 trials with sibutramine that were considered of sufficiently high quality for inclusion in the analysis [91]. Sibutramine was more effective than placebo in promoting weight loss in overweight and obese adults at all time points assessed, from 8 weeks up to 54 weeks. A Cochrane systematic review included five high-quality sibutramine weight loss studies over one year (three weight loss and two weight maintenance trials) [79]. Attrition rates averaged 43% during the weight loss phase. Compared to placebo, sibutramine-treated patients lost 4.3 kg (95% CI : 3.6 to 4.9 kg). The number of patients achieving 10% or greater weight loss was 15% (95% CI : 4 to 27%) higher with sibutramine than with placebo. In the STORM ("Sibutramine Trial of Obesity Reduction and Maintenance") study, an individualised management programme combining restricted diet and sibutramine achieved weight loss in almost 75% of obese patients after 6 months and sustained weight loss in around 50% of patients continuing therapy for 2 years [92]. A Cochrane review on the use of pharmacotherapy for weight loss in adults with T2DM revealed that sibutramine produced significant reductions in body weight (5.1 kg; 95% CI 3.2-7.0) at 12 to 52 weeks follow-up [82]. However, despite this weight reduction, the average impact on HbA1c was rather modest [93], except in patients with the largest weight reduction, possibly because of drug-associated sympathetic activation [83].

There is no direct evidence that sibutramine reduces the incidence of new-onset diabetes in overweight/obese patients. A long-term large-scale prospective trial (« Sibutramine Cardiovascular and Diabetes Outcome Study » or SCOUT) has been designed to determine whether weight management with a novel lifestyle intervention plus either sibutramine (10-15 mg/day) or placebo in cardiovascular high-risk overweight and obese patients can impact upon cardiovascular endpoints [94]. To be eligible for inclusion, patients must have experienced a cardiovascular event or have diagnosed T2DM and another cardiovascular risk factor. The primary endpoint of the trial will include a composite cardiovascular endpoint. Because of the size of the study (almost 9,000 patients followed for at least 3 years), informative data on the effect of sibutramine on the risk of developing T2DM might also be obtained from this trial.

3.3. Rimonabant

Rimonabant is the first selective CB1 receptor blocker launched for the treatment of overweight/obese subjects with risk factor(s), such as T2DM and dyslipidaemia. The endocannabinoid (EC) system, consisting of the cannabinoid type 1 (CB_1) receptor and endogenous lipid-derived ligands, appears to modulate energy homeostasis as well as glucose and lipid

metabolism, both through central orexigenic effects and peripheral metabolic effects in adipose tissue, liver, skeletal muscle and pancreas [95,96]. In non-diabetic overweight/obese patients, rimonabant 20 mg, as compared to placebo, has been shown to produce significant weight loss and waist circumference reduction, the latter being a key marker of intra-abdominal adiposity, and improvements in multiple cardiometabolic risk factors. Besides a significant increase in HDL cholesterol and a significant decrease in triglyceride levels, improvements in glucose metabolism have been described, with a reduction in high fasting insulin levels and HOMA insulin resistance index [97-99]. In a 1-year trial performed in overweight/obese patients with diabetes, all these effects were confirmed and, in addition, a placebo-subtracted 0.7% reduction in HbA1c levels was observed [100]. Almost half of these metabolic effects occur beyond weight loss [101]. Part of these metabolic improvements may be attributed to a significant increase in plasma adiponectin levels [98]. Rimonabant also improves glucose tolerance and reduces post-glucose load plasma insulin response in both RIO-Europe [97] and RIO-Lipids [98]. The favourable effects on plasma glucose and insulin levels observed with rimonabant 20 mg after one year persisted after two years in the RIO-Europe trial [102]. In a pooled post-hoc analysis of the three RCTs performed in non-diabetic patients, more obese subjects improved glucose tolerance and fewer individuals progressed towards T2DM in the rimonabant 20 mg group as compared to the placebo group [103]. The ongoing RAPSODI ("Rimonabant in Pre-Diabetic Subjects to Delay Onset of Type 2 Diabetes") two-year trial has enrolled 2,100 participants, with researchers specifically focusing on whether rimonabant 20 mg helps prevent T2DM in patients with pre-diabetes in the form of IFG and/or IGT.

4. PREVENTION BY LIPID-LOWERING AGENTS (Figure 2)

There is an intimate relationship between glucose and lipid metabolism [104]. Especially, high circulating levels of free fatty acid [105] and ectopic depots of triglycerides in various organs such as liver, skeletal muscle, and pancreas [106] have been shown to be associated with increased insulin resistance and impaired insulin secretion, leading to the concept of lipotoxicity [33]. Therefore, drugs interfering with lipid metabolism may exert favourable effects on glucose metabolism and possibly prevent the progression from IGT to T2DM. However, despite some anecdotal small-sized trials, there is no convincing and consistent evidence of a favourable effect of statins [107] or fibrates [108,109] on insulin sensitivity, and nicotinic acid has been shown to be associated with impaired rather than improved insulin sensitivity [110].

4.1. Statins

Statins act by inhibiting of HMG-CoA reductase, a key-enzyme in the synthesis of cholesterol in the hepatocytes. Besides the remarkable reduction in total and LDL cholesterol levels, they exert numerous pleiotropic effects, which may explain their favourable effect of prevention of cardiovascular events [111]. Even if they are recognized to improve endothelial function and to reduce low-grade inflammation, statins do not exert strong beneficial effects on insulin sensitivity, although some studies reported a significant reduction of insulin resistance after statin therapy [107]. In a post hoc analysis from the West of Scotland Coronary Prevention Study (WOSCOPS), diabetes incidence was significantly lower with pravastatin treatment compared to placebo (1.9% versus 2.8%, RR = 0.70, 95% CI 0.50-0.99) [112]. However, the rate of progression to T2DM was low in this trial, leading to a low number of events, the prevalence of IGT at entry into the study was unknown and the diagnosis of diabetes was only based on self-reporting or a fasting glucose level $\geq$ 7.0 mmol/l. In three other post hoc analyses of large placebo-controlled statin cardiovascular trials, no significant reduction in the incidence of new T2DM was observed with the cholesterol-lowering drug : with simvastatin in the "Heart Protection Study" (HPS) (4.6% versus 4.0%, 95% CI 1.15, 0.99-1-34) [113], with pravastatin in the "Long-Term Intervention with Pravastatin in Ischemic Disease" (LIPID) study (4.0% versus 4.5%, 0.89, 95% CI 0.70-1.13) [114], and with atorvastatin in the "Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowerig Arm" (ASCOT-LLA) (3.0% versus 2.6%, RR= 1.15, 95% CI 0.91-1.44) [115]. Therefore, there is no current evidence supporting a significant effect of a statin therapy to prevent the development of T2DM.

A retrospective cohort study using Saskatchewan health databases to identify subjects newly started on oral antidiabetic agents from 1991 to 1996 showed that the use of statins is associated with an average 10-month delay in starting insulin treatment in 10,996 patients with T2DM initially treated with oral antidiabetic agents [116]. However, after 7 years of follow-up, there were no differences between the statin and control groups in their requirements for insulin therapy. The Authors asked whether this protection also exists for patients at high risk of developing diabetes. A nested case-control study based on data from the UK-based General Practice research database concluded that there is little if any protective effect of statins on the development of T2DM [117].

4.2 Fibrates

Because of their specific mechanism of action on PPAR-alpha receptors and their effects on circulating triglyceride and free fatty acid levels (FFA), fibrate derivatives may exert more favourable effects on glucose metabolism than statins [118]. However, previous studies have yielded conflicting results for effects of fibrates on glycaemic control, and both bezafibrate [108] and gemfibrozil [109]

were reported to have no effect on insulin resistance. Nevertheless, in the "Bezafibrate Infarction Prevention" (BIP) trial, a post hoc analysis of 303 patients with IGT showed that bezafibrate therapy was associated with a significant reduction in T2DM incidence compared with placebo (HR = 0.70, 95% CI 0.49-0.99) [119]. However, no other trials reported similar favourable results with other fibrates, either gemfibrozil or fenofibrate, so that such possible effects of fibrates to avoid progression to T2DM require further confirmation.

4.3. Nicotinic acid

Unexpectedly, despite its inhibitory effect on lipolysis and its lowering action on FFA levels, nicotinic acid has been shown to be associated with increased insulin resistance rather than improved insulin sensitivity. This effect, probably due to a marked rebound in plasma free fatty acid concentrations, requires increased insulin secretion to maintain normal glucose tolerance and may lead to IGT [110]. Prolonged-release nicotinic acid has improved tolerability as compared to nicotinic acid and exerts less deterioration of insulin sensitivity and glucose tolerance, presumably because a less marked rebound in plasma FFA levels [120]. Although it may be used in the management of dyslipidaemia associated with diabetes and metabolic syndrome [121], there is no evidence that it may prevent T2DM in patients with IGT and there is no ongoing trial trying to demonstrate such a protective effect.

5. EFFECTS OF RAAS INHIBITION ON DEVELOPMENT OF DIABETES (Figure 2)

During recent years, there is a growing interest for the ability to prevent T2DM by the inhibition of the RAAS [33,122-124]. It is well known that the risk of new-onset diabetes is increased in patients with arterial hypertension. The risk is even greater in patients receiving antihypertensive therapy although this may largely vary according to the type of antihypertensive agents used. To this respect, old antihypertensive medications such as diuretics and beta-blockers are more deleterious than new agents such as calcium channel antagonists and RAAS inhibitors [125-128].

The inhibition of the RAAS has been shown to be associated with various metabolic effects that may contribute to protect against the development of T2DM [129]. It resulted in improvement of insulin sensitivity in some studies [33,130]. However, the data were heterogeneous across the trials and tended to be less consistent with ARBs than with ACE inhibitors. In fact, the effects of ACE inhibition on glucose tolerance are more consistent than those on insulin sensitivity. Many reports in non-diabetic patients have found some improvement in glucose tolerance, whether assessed by the OGTT or judged from fasting plasma glucose or glycated haemoglobin levels [review in 33]. Recent data brought

support for a positive effect of RAAS inhibition on B-cell function and insulin secretion as well [131,132]. It remains to be established the extent to which these metabolic effects will influence the long-term consequences for future risk of T2DM, especially in at risk populations such as patients with arterial hypertension, congestive heart failure or coronary heart disease treated with either ACE inhibitors or ARBs [133].

5.1. ACE inhibitors

At least nine trials have examined as a secondary outcome the effect of ACE inhibitors on the prevention of T2DM in high risk population [33,122-124]. Most studies were performed in patients with arterial hypertension. Except in the STOP-Hypertension-2 study [134] comparing enalapril/lisinopril with beta-blocker, a significant reduction in the incidence of new-onset diabetes was observed in patients receiving an ACE inhibitor versus patients receiving a comparator, either placebo or an active drug (table 2) : "Captopril Prevention Project" (CAPPP) comparing captopril versus conventional treatment with beta-blockers or diuretics [135]; "Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial" (ALLHAT) comparing lisinopril versus chlorthalidone or lisinopril versus amlodipine [136]; "2nd Australian National Blood Pressure Study" (ANBP2) comparing enalapril versus hydrochlorothiazide [137]; "Anglo-Scandinavian Cardiac Outcomes Trial" (ASCOT) comparing perindopril (added as required to amlodipine) versus atenolol (added as required to bendroflumethiazide) [138]. Three studies [139-141] were performed in patients with coronary heart disease, with a significant reduction in two out of them [139,140]: "Prevention of Events with Angiotensin Converting Enzyme Inhibition" (PEACE) comparing trandolapril versus placebo [139], "International Verapamil-Trandolapril Study" (INVEST) comparing a verapamil sustained release/trandolapril (trandolapril as add-on therapy) strategy versus an atenolol/hydrochlorothiazide strategy [140], "EUropean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease" (EUROPA) comparing perindopril with placebo [141]. The "Heart Outcomes Prevention Evaluation" (HOPE) trial recruited patients with high cardiovascular risk, because of arterial hypertension or the presence of other cardiovascular risk factors and compared ramipril with placebo [142,143]. A post-hoc analysis reported a remarkable 35% RRR reduction of new onset T2DM with ramipril as compared with placebo at the end of 4.5 year follow up. Interestingly, during a 2.6 year extension study, there was a significant further reduction in risk of diabetes for patients in the ramipril group versus in the placebo group (RR = 0.66; 95% CI 0.46-0.95) [144]. Thus, the benefits observed during the HOPE trial was sustained during passive follow-up despite late similar rates of ACEI use in the two randomized groups. Considering the combined in-trial period and post-trial follow-up of 7.2

years, there was a 31% RRR in new diagnoses of T2DM in the ramipril group as compared to the placebo group. Only one study concerned patients with congestive heart failure. In a retrospective study assessing the effect of the ACE inhibitor enalapril on the incidence of diabetes in a small subgroup of the "Studies Of Left Ventricular Dysfunction" (SOLVD) [145], a dramatic reduction of new cases of T2DM was noticed in patients treated with enalapril as compared to those receiving placebo. By multivariate analysis, enalapril was the most powerful predictor for risk reduction of developing T2DM (RR = 0.22; 95 % CI 0.10 to 0.46; p < 0.0001). Despite this almost remarkable consistency of the observations, it should be pointed out, however, that all these results were the product of a post hoc analysis or the secondary results of trials projected for a different scope, i.e. cardiovascular protection, and obtained using heterogeneous criteria for diabetes diagnosis. Unfortunately, the prevalence of IGT is unknown in those study populations. Thus, the consistent positive findings that ACE inhibitors may prevent T2DM should receive a definite answer after completion of large-scale trials specifically devoted to answer this important question.

As already mentioned, the DREAM ("Diabetes REduction Approaches with ramipril and rosiglitazone Medications") trial was designed to evaluate prospectively whether ramipril 15 mg od prevents T2DM among individuals at high risk because of IGT or IFG [146]. After a median follow-up of 3 years in 5269 participants, the incidence of the primary outcome (effects of ramipril on the development of T2DM or death) did not differ significantly between the ramipril group (18.1%) and the placebo group (19.5%; HR = 0.91; 95% CI 0.81-1.03; p =0.15). However, participants receiving ramipril were more likely to have regression to normoglycaemia (a prespecified secondary outcome) than those receiving placebo (HR = 1.16, 95% CI 1.07-1.27; p = 0.001). Thus, among persons with IGT or IFG, the use of ramipril for 3 years does not significantly reduce the incidence of T2DM or death but does significantly increase regression to normoglycaemia. There may be several reasons why the results of DREAM differ from the reductions in the rates of newly diagnosed diabetes reported previously with ACE inhibitors. Besides the use of a more rigorous protocol concerning the definition of diabetes and its screening at baseline and during the study, it is of note that participants of DREAM differed from those of previous studies, who were older and primarily had known cardiovascular disease, heart failure, hypertension, or a combination thereof. It is possible that the degree of activation of the RAAS is higher in the latter patients and that the ACE inhibition may therefore have a greater effect in these people than in others as those recruited in DREAM. Thus, ACE inhibitors are not recommended to prevent T2DM in absence of other cardiovascular risk factors [147]. Nevertheless, the results of DREAM suggest that ramipril may have favourable effects on glucose metabolism (mild reduction in glucose levels and higher conversion rate to normal glucose tolerance), a finding that is consonant with

other reports on studies of ACE inhibitors.

5.2. Angiotensin receptor blockers

At least four studies assessed the efficacy of an ARB and three out of them demonstrated a significant reduction in new cases of T2DM in hypertensive patients as compared to a placebo or an other active antihypertensive drug [33,122-124] : "Losartan Intervention For Endpoint reduction in hypertension study" (LIFE) comparing losartan with atenolol [148,149]; "Antihypertensive treatment and Lipid Profile In a North of Sweden Efficacy Evaluation" (ALPINE) comparing candesartan with hydrochlorothiazide [150]; "Valsartan Amlodipine Long-Term Use Evaluation" (VALUE) comparing valsartan and amlodipine [151]. Only the "Study on Cognition and Prognosis in the Elderly" (SCOPE) comparing candesartan versus placebo showed a 25% difference that did not reach statistical significance [152]. These observations in hypertensive individuals were confirmed in one trial in patients with congestive heart failure, the "Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity" (CHARM) study [153,154]. After a mean follow-up of 37.7 months, the number of newly diagnosed patients as having diabetes was significantly lower with candesartan (6%) than with placebo (7%) : HR = 0.78; 95% CI, 0.64-0.96; p = 0.020. There is therefore enough circumstantial evidence to justify a prospective study on the effect of ARB on the prevention of T2DM in high risk population.

The NAVIGATOR ("Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research") is an international randomized placebo-controlled 2x2 factorial design to assess the effect of nateglinide (see above 2.2) and/or valsartan on the prevention of T2DM and cardiovascular events as primary outcomes in subjects with IGT and high risk for cardiovascular disease [56]. The diagnosis of diabetes is based on the OGTT. More than 9,500 individuals were recruited and will be followed for 3 years. The results should be available in 2007. ONTARGET ("Telmisartan Alone and in combination with Ramipril Global Endpoint trial") is a three-arm study testing telmisartan, ramipril and telmisartan plus ramipril on cardiovascular events in a high risk population of 22,440 subjects [155]. Those individuals who cannot tolerate ACE inhibitors will be enrolled in a parallel study, TRANSCEND ("Telmisartan RANdomized assessment Study in angiotensin inhibitor intolerant patients with cardiovascular Disease") which will compare telmisartan with placebo in almost 5,000 individuals. The ONTARGET-TRANSCEND studies will also look at the effect of those treatments on the development of T2DM based on fasting plasma glucose as a prespecified secondary outcome. ONTARGET will also offer the unique opportunity to compare the effects of an ACE inhibitor and an ARB in a head-to-head trial and to investigate the potential of any additional effect of an ACE inhibitor-ARB combination to

prevent T2DM as compared to monotherapy. The use of telmisartan is also of special interest as this highly lipophilic ARB has been shown to exert partial PPAR-γ activity (selective PPAR modulator or SPPARM), thus an effect related to glitazones, which may bring an add-on value for the prevention of T2DM [156,157]. The results should be available in 2007-2008, after a mean follow-up of 5.5 years.

In conclusion, there is growing and consistent evidence that RAAS inhibition may prevent the development of T2DM in high-risk individuals. Indirect comparison suggests that ACE inhibitors and ARBs have a similar and significant ability to reduce the occurrence of new-onset T2DM among subjects with arterial hypertension, congestive heart failure and coronary heart disease [33, 122-124, 133]. Therefore, an ACE inhibitor or ARB is a logical first-line antihypertensive therapy in patients with IFG or metabolic syndrome for multiple reasons, including the reduction of risk of progression to overt T2DM. Obviously, part of the antidiabetic mechanisms occurs beyond the RAAS [158]. However, as shown recently by the results of DREAM, the routine use of ACE inhibitor such as ramipril for the express purpose of preventing diabetes, in absence of cardiovascular disease, is not indicated.

6. PREVENTION BY VARIOUS DRUGS (Figure 2)

6.1. Estrogen

There is increasing evidence both in rodents and in humans linking the endogenous estrogen 17β-estradiol (E2) to the maintenance of glucose homeostasis [159,160]. Five cohort studies, which have examined the association between estrogen use and T2DM incidence, reported controversial results [28]. However, several trials failed to adjust for potentially important covariates such as family history of T2DM, body weight, or baseline glucose measurements. The Nurses Health Study, the largest of the cohort studies, found that over 12 years, current estrogen use was associated with a significant reduction in T2DM incidence compared with never users, but no difference between former estrogen users and never users [161] (Table 4). In the Strong Heart Study in American Indian postmenopausal women, the risk of T2DM was not significantly increased when comparing current users versus past or never users, but increased modestly with increasing duration of estrogen use among current users, with an odds ratio of 1.10 per year of use [162]. In contrast, a recent study revealed that transdermal 17-β-estradiol significantly reduced the risk of developing T2DM in healthy, nonobese, postmenopausal [163] (Table 4).

The two most important data result from post hoc analysis of the HERS ("Heart and Estrogen/Progestin Replacement Study") [164] and WHI ("Women's Health Initiative Hormone Trial")

studies [165,166]. In HERS, combination estrogen and progesterone therapy was associated with a significant reduction in the incidence of T2DM from 9.0 to 6.2% compared with placebo (RR = 0.65) [164]. In the WHI Trial, the cumulative incidence of treated diabetes after 5.6 years of follow-up was 3.5% in the hormone therapy group (daily 0.625 mg conjugated equine oestrogens plus 2.5 mg medroxyprogesterone acetate) and 4.2% in the placebo group (HR = 0.79) [165]. However, there was little change in the HR after adjustment for changes in BMI and waist circumference. During the first year of follow-up, changes in fasting and insulin levels indicated a significant fall in insulin resistance in actively treated women compared with the control group. In a substudy of this large trial, the effect of daily 0.625 mg conjugated equine oestrogen alone were compared to placebo in women who had previously had a hysterectomy [166]. After a mean 7.1-year follow-up, the cumulative incidence of treated T2DM was 8.3% in the oestrogen-alone group and 9.3% in the placebo group (HR 0.88, p = 0.072) (Table 4). A significant reduction in insulin resistance assessed by the HOMA-model was observed after 1 year, but not after 3 and 6 years of follow-up. Therefore, the effect appears to be smaller with oestrogen alone than that seen with oestrogen plus progestin.

These recent data suggest that combined therapy with estrogen and progestin reduces the incidence of T2DM, possibly by a decrease in insulin resistance unrelated to body size. However, in view of the overall adverse effects of this combination, especially the increased risk of cardiovascular disease, it is not justified to use combined estrogen plus progestin therapy for the prevention of T2DM in postmenopausal women. Nevertheless, further study of mechanisms seems warranted to explore the role of hormonal factors in diabetes prevention. Recent data from the Rancho Bernardo Study showed that proinsulin, but not insulin, levels were significantly lower in current hormone replacement therapy users than in previous and never hormone replacement therapy users [167]. Proinsulin reflects insulin resistance more than intact insulin and hyperproinsulinaemia may be a sign of a pancreatic B-cell defect, augmented by an increased demand placed on the B cell. The effects of estrogen on insulin secretion merit further investigation and might lead to new therapies [168]. Further studies of alternative postmenopausal hormone therapy regimens and selective estrogen agonists and/or antagonists should consider the effects of these regimens on insulin resistance, insulin secretion and new-onset T2DM.

6.2. Anti-inflammatory drugs

There is a growing body of evidence for the role of inflammation in insulin resistance and T2DM [169-171]. More than 15 studies in different ethnic groups have shown a remarkable consistency in demonstrating that high sensitive C-reactive protein (hs-CRP), interleukin-6 (Il-6) and

some other inflammatory markers predict the development of T2DM [172-176]. For example, an overall inflammation score based on four inflammatory markers plus white cell count and fibrinogen predicted diabetes in the Atherosclerosis Risk in Communities Study participants [177]. In general, the predictive power of hs-CRP, the most widely used marker, was somewhat stronger than that of Il-6. However, it was reduced after adjustment for BMI or other factors related to insulin resistance, although it remained a significant independent risk marker in most studies. In addition, almost 10 prospective studies have demonstrated that low adiponectin levels predict an increased incidence of T2DM [178]. For instance, in the Atherosclerosis Risk in Communities Study, a case-cohort study representing the approximately 9-year experience of 10,275 middle-aged US participants, hazard ratios (95% CIs) for developing T2DM, for those in the second, third and fourth (versus the first) quartile of adiponectin were 0.72 (0.48-1.09), 0.67 (0.43-1.04) and 0.58 (0.34-0.99), respectively, after extensive adjustments for all known confounding risk factors [179]. Thus, there is accumulating evidence suggesting that inflammation is the bridging link between obesity, T2DM and atherosclerosis. Thus, interventions using agents with anti-inflammatory properties may reduce the risk of both conditions.

Evidence is emerging that many drugs that may reduce the incidence and/or delay the onset of T2DM have apparent "anti-inflammatory" properties [180]. It is the case for thiazolidinediones, metformin, ACE inhibitors, ARBs, fibrates and statins, which all are able to reduce hs-CRP levels and other inflammatory markers [181]. However, although all these drugs with potential anti-inflammatory properties reduce the risk of developing T2DM, it is difficult to prove whether such anti-inflammatory properties contribute to their diabetes prevention effect and, if yes, to what extent. Indeed, nearly all drugs have other, often more pronounced, metabolic actions that can explain the prevention effect of T2DM. Thus, only specific trials wit drugs exerting specific anti-inflammatory effects may answer the question. High-dose aspirin inhibits cyclooxygenase and IkappaB kinase-beta and reduces fasting plasma glucose concentration in patients with T2DM [182]. While controversial results about the effect of acetylsalicylic acid on insulin resistance have been reported, a recent study in healthy men showed that acetylsalicylic acid specifically attenuates the lipid-induced insulin resistance, but not insulin resistance in absence of high lipid levels [183]. However, this beneficial effect of ASA was not accompanied by any changes in inflammatory markers. Unfortunately, there has not, as yet, been a large-scale trial to examine the effect of aspirin on the risk of developing T2DM. Clinical trials to test efficacy, tolerability, and durability of salsalate (nonacetylated salicylate) are currently being undertaken in the NIH-funded TINSAL-T2DM and cardiovascular trials (Targeting Inflammation with Salsalate in T2DM and cardiovascular disease, respectively). Other more specific anti-inflammatory strategies (JNK or IKKβ inhibitors, compounds that block TNF-a, IL-6, TLR or chemokine signalling)

are being considered, but these studies are at much earlier stages [171]. Studies with these novel inhibitors of inflammatory pathways will help determine whether targeting the inflammation axis is a fertile mechanism to prevent (or treat) T2DM [181].

6. CONCLUSION

The goal of ultimately reducing the population burden of diabetes by early treatment and prevention is clearly of pivotal importance. Obviously, intensive lifestyle intervention is the mainstay for the prevention of T2DM given the remarkable reduction in the incidence of T2DM, the prolonged benefits, the demonstrable cost effectiveness and the absence of adverse events. Unfortunately, intensive lifestyle intervention is difficult to implement and to sustain in most individuals and many subjects will still progress to T2DM. Besides life-style modifications, pharmacological strategies using various glucose-lowering agents, antiobesity drugs and compounds that inhibit RAAS activity might be considered as a valuable alternative. Owing to the pathophysiology of T2DM, these drugs must act either by reducing insulin resistance and/or by improving insulin secretion, with a special interest in the protection of beta cells. The effects of lipid-lowering agents are more controversial so that these compounds should be used for their cardiovascular protection but not for diabetes prevention. Although estrogen use is controversial as far as cardiovascular prevention is concerned, increasing evidence suggests that estrogen may prevent T2DM in post-menopausal women. As chronic inflammation seems to play a role in the pathophysiology of T2DM, it is plausible that new compounds will emerge in a near future targeting this abnormality. As far as glucose-lowering agents are concerned, an at least partial masking effect should be excluded because most results were obtained either when subjects were still on the drug or after a rather short washout period. In addition, because T2DM is a progressive disease, it remains to be established in long-term studies whether the so-called preventing effect is not simply a postponing effect.

It is of note that no pharmacological agent is currently approved for the particular indication of diabetes prevention. However, because so many different pharmacological approaches may be theoretically used, a practical key question would be which one should be chosen for each patient. Besides the phenotype of the patient, it is expected that genotype studies will help in the selection in a near future. Another interesting question is whether combined drug therapy may add further protection against new-onset diabetes. Although no additive protection was observed in the DREAM study with the rosiglitazone-ramipril combination as compared to rosiglitazone alone, new ongoing trials assessing the potential of various other combinations (metformin + rosiglitazone, nateglinide + valsartan,

telmisartan + ramipril) would provide partial answer to this last question. Finally, all available data and ongoing trials are limited to the middle-aged or elderly population. The prevalence of diabetes is growing rapidly in adolescents so that preventive measures, including pharmacological approaches when necessary, should be implemented rapidly among paediatric patients and presumable should target first overweight/obese young people with a family history of T2DM. However, long-term benefits from preventing new-onset diabetes, although easily conceivable, remain to be demonstrated in the future.

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FIGURES

Figure 1 : Illustration of the sites of action of oral glucose-lowering agents used in the various clinical trials of prevention of type 2 diabetes in high risk patients (mainly because of impaired glucose tolerance)

Figure 2 : Various hypothetical mechanisms implicated in the pathogenesis of type 2 diabetes and illustration of the sites of action of non-glucose-lowering agents considered for the prevention of type 2 diabetes in high risk patients

Table 1 : Placebo-controlled randomised clinical trials assessing the effect of metformin, acarbose, and thiazolidinediones on the incidence of new-onset diabetes in patients with impaired glucose tolerance. F-U : follow-up. RR : relative risk of developing diabetes versus placebo. 95% CI :95% confidence interval. NA : not available

Trial [Reference]	Drug	Daily dose mg	F-U years	n	RR (95% CI)	p
US DPP [18]	Metformin	850 mg b.i.d.	2.8	2155	0.69 (0.57-0.83)	0.001
CDPS [44]	Metformin	250 mg t.i.d.	3	261	0.23 (NA)	0.0002
EDIT [45]	Metformin	500 mg t.i.d.	6	631	0.99 (NA)	0.94
Indian DPP [46]	Metformin	250 mg b.i.d.	2.5	531	0.74 (0.65-0.81)	0.029
TRIPOD [61]	Troglitazone	400 mg o.d.	2.5	236	0.45 (0.25-0.83)	0.01
US DPP [65]	Troglitazone	400 mg o.d.	0.9	585	0.25 (NA)	0.02
DREAM [66]	Rosiglitazone	8 mg o.d.	3.0	5269	0.40 (0.35-0.46)	0.0001
STOP-NIDDM [71]	Acarbose	100 mg t.i.d.	3.2	1368	0.75 (0.63-0.90)	0.0015
CDPS [44]	Acarbose	50 mg t.i.d.	3	261	0.12 (NA)	0.00001
EDIT [45]	Acarbose	50 mg t.i.d.	6	631	1.04 (NA)	0.81
	Acarbose	50 mg t.i.d.	6	? (*)	0.66 (NA)	0.046

(*)   Subgroup of patients (n = NA) with impaired glucose tolerance (IGT) at baseline

Table 2 : Randomised clinical trials assessing the effect of ACE inhibitors (ACEI) on the incidence of diabetes in high-risk patients with hypertension, congestive heart failure and coronary artery disease. In the bottom, results of the DREAM study performed in patients without high cardiovascular risk. F-U : follow-up. RR : relative risk of developing diabetes versus comparator. 95% CI : 95% confidence interval. HCTZ : hydrochlorothiazide. NA = not available. NS : not significant.

Trial [Reference]	n	ACEI	Comparator	F-U years	RR (95% CI)	p
STOP-HTN2 [134]	6,614	Enalapril/lisinopril	β-blocker	5.0	0.96 (0.72-1.27)	NS
CAPPP [135]	10,985	Captopril	β-blocker-diuretic	6.1	0.79 (0.67-0.94)	0.039
ALLHAT [136]	33,357	Lisinopril	Chlorthalidone	4.9	0.70 (0.56-0.86)	0.001
ALLHAT [136]	33,357	Lisinopril	Amlodipine	4.9	0.83 (0.74-0.93)	0.001
ANBP2 [138]	6,083	Enalapril (*)	HCTZ	4.1	0.66 (0.54-0.85)	0.001
ASCOT [137]	19.257	Perindopril	Atenolol	5.5	0.70 (0.63-0.78)	0.001
PEACE [139]	8,290	Trandolapril (*)	Placebo	4.8	0.83 (0.72-0.96)	0.001
INVEST [140]	16,176	Trandolapril	HCTZ	2.7	0.85 (0.77-0.95)	0.001
EUROPA [141]	12,228	Perindopril (*)	Placebo	4.2	0.97 (NA)	NS
HOPE [142,143]	9,297	Ramipril	Placebo	5.0	0.66 (0.51-0.85)	0.001
SOLVD [145] (**)	4,228	Enalapril	Placebo	3.4	0.26 (0.13-0.53)	0.0001
DREAM [146] (***)	5,269	Ramipril	Placebo	3.0	0.91 (0.80-1.03)	NS

(*)   ACE inhibitor as add-on therapy
(**)   Patients with congestive heart failure
(***)   Individuals without cardiovascular disease

Table 3 : Randomised clinical trials assessing the effect of angiotensin receptor blockers (ARB) on the incidence of diabetes in high-risk patients with hypertension, congestive heart failure and coronary artery disease. F-U : follow-up. RR : relative risk of developing diabetes versus comparator. 95% CI : 95% confidence interval.

Trial [Reference]	n	ARB	Comparator	F-U years	Relative risk (RR) (95% CI)	p
LIFE [148,149]	9,193	Losartan	Atenolol	4.8	0.75 (0.63-0.88)	0.001
ALPINE [150]	392	Candesartan	Atenolol	1.0	0.13 (0.03-0.99)	0.03
VALUE [151]	15,245	Valsartan	Amlodipine	4.2	0.77 (0.69-0.86)	0.0001
SCOPE [152]	4,937	Candesartan	Placebo	3.7	0.81 (0.61-1.02)	0.09
CHARM [153,154] (*)	7,599	Candesartan	Placebo	3.2	0.78 (0.64-0.96)	0.02

(*)   Patients with congestive heart failure

Table 4 : Clinical studies assessing the effect of estrogen replacement therapy on the incidence of new-onset diabetes in post-menopausal women. 95% CI : 95% confidence interval.

Reference	n	FU (years)	Relative risk	95% CI	p
Manson et al 1992 [161]	21,028	12.0	0.80	0.67-0.96	0.005
Zhang et al 2002 [162]	857	4.0	1.11	0.62-1.97	NS
Kanaya et al 2003 [164]	2,029	4.1	0.65	0.48-0.89	0.006
Margolis et al 2004 [165]	15,641	5.6	0.79	0.67-0.93	0.004
Rossi et al 2004 [163] (**)	673	3.7	0.45	0.29-0.56	0.001
Bonds et al 2006 [166] (***)	10,739	7.1	0.88	0.77-1.01	0.072

(*) In this study, the risk of D2TM increased with increasing duration of estrogen use among current users

(**) Only trial performed with transdermal 17-β-estradiol instead of oral conjugated estrogen therapy

(***) Estrogen alone (without progestin)