

# Strategies to Prevent Type 2 Diabetes

## Abstract and Introduction

### Abstract

Type 2 diabetes mellitus is a public health problem of epidemic proportions and its prevalence is on the rise. The typical American born today has a one in three chance of developing type 2 diabetes. This diagnosis is associated with an adverse cardiovascular prognosis and is considered the risk equivalent of established coronary disease. Many risk factors, including the metabolic syndrome, have been implicated in its development. Even in high-risk individuals, type 2 diabetes is a preventable disease. Diet and exercise have been consistently shown to decrease the incidence of diabetes in large randomized controlled studies. Additionally, new-onset diabetes was reduced by several oral pharmacologic anti-diabetic agents including metformin, acarbose and troglitazone in randomized trials which studied patients with impaired glucose tolerance. More interestingly, multiple large prospective studies have also reported a reduction in the development of type 2 diabetes in patients treated with antihypertensive agents, predominantly angiotensin converting enzyme inhibitors and angiotensin receptor blockers.

In this review, we will discuss some of these important trials and the speculative mechanisms whereby those medications prevent type 2 diabetes. Such observations, if proven to be true, may represent preventive strategies which can be considered in patients with pre-diabetic conditions such as the metabolic syndrome, hypertension, impaired fasting glucose, family history of diabetes, obesity, congestive heart failure or other risks for the development of type 2 diabetes.

### Introduction

Diabetes mellitus is a public health problem of epidemic proportions, and its prevalence is on the rise. More than 19 million adults in the United States and 150 million worldwide have diabetes; by the year 2025, the World Health Organization projects more than 300 million cases worldwide.<sup>[1]</sup>

The health and economic ramifications of diabetes are vast and ominous for the individual diagnosed with the disease as well as for society at large. Many risk factors, including the increasingly prevalent metabolic syndrome, have been implicated in its development.<sup>[2]</sup> Even in high risk individuals, type 2 diabetes is a preventable disease.

Insulin resistance is the major underlying pathophysiologic defect leading to the development of type 2 diabetes.<sup>[3]</sup> Yet approximately two-thirds of people with insulin resistance do not go on to develop overt type 2 diabetes, but are nevertheless at almost the same increased risk of cardiovascular events as diabetic individuals.<sup>[4]</sup> Improving insulin sensitivity through diet and exercise has been found to decrease the incidence of diabetes and lower cardiovascular events in randomized controlled trials.<sup>[5-7]</sup> Additionally, several oral anti-diabetic agents, as well as an anti-obesity agent, have been shown to offer a similar and possibly an added benefit.<sup>[5,8-11]</sup> More

recently, some anti-hypertensive drugs were also found to reduce the risk of developing diabetes.<sup>[12-27]</sup>

In this review, we will try to discuss diabetes as one of the century's largest epidemics, its risk factors and the potential interventions available to prevent its progression. We will also shed light on the mechanisms, though speculative, that account for such a remarkable effect of these interventions, mainly the use of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).

Studies which reported the incidence of new-onset diabetes with the use of different medications were identified through a systematic review of the published literature from January 1990-December 2004 using MEDLINE, EMBASE and the Cochrane Library. The following indexing terms were used: (diabetes mellitus, type 2), new\$ or emerg\$ or prevent\$ or develop\$ or risk\$, hypoglycemic agents, anti-obesity agents and anti-hypertensive agents. A manual review of the bibliographies of seminal primary and review articles was also performed to identify any additional relevant studies.

Only randomized trials were retrieved and only if they met the following criteria: duration of at least 1 year, subjects had impaired glucose tolerance, hypertension or any other cardiovascular risk factor and the incidence of new-onset diabetes was reported in the treatment and control groups for those patients without diabetes at baseline.

## **The Growing Epidemic of Diabetes**

More than 150 million people worldwide have diabetes, and this number is expected to double by the year 2025.<sup>[1]</sup> An American born today has a one in three chance of developing type 2 diabetes during his lifetime; for Hispanics and African-Americans, the risk is almost one in two. For a male diagnosed with diabetes at age 40 years, average life expectancy is reduced by approximately 11.6 years and quality years reduced by 18.6 years.<sup>[28]</sup> A diagnosis of type 2 diabetes carries adverse prognostic implications since 70% of diabetic patients die from cardiovascular disease and two thirds of these as a result of coronary heart disease (CHD). Therefore, the National Cholesterol Education Panel considers diabetes a CHD equivalent since, over a decade, 20% of diabetic subjects will have a cardiac event.<sup>[29]</sup> This is a similar risk to that of peripheral vascular disease, cerebrovascular disease or the presence of an aortic aneurysm. Strategies to prevent type 2 diabetes are of paramount importance in improving the health of the American population in the 21st century.

## **Risk Factors for Diabetes**

Risk factors for the development of type 2 diabetes are shown in [Table 1](#). The recently characterized constellation of risk factors referred to as the metabolic syndrome (due to underlying insulin resistance) is a wellrecognized precursor to the development of diabetes.<sup>[30,31]</sup> However, these patients are also at high risk for cardiovascular events due to accelerated atherosclerosis, hypercoagulability, dyslipidemia and endothelial dysfunction even if they do not develop diabetes.<sup>[30,31]</sup> Approximately 24% (47 million) of adult Americans have the metabolic syndrome. The prevalence of this disorder is rising sharply and in parallel with the obesity

epidemic. Over age 60 years, 44% have this syndrome, with Mexican-Americans having the highest age-adjusted prevalence (31.9%).<sup>[32,33]</sup>

## **Role of Insulin Resistance**

Insulin resistance plays a causal role in hypertension and atherosclerosis, and therefore is present in the majority of patients with these conditions. About 50% of hypertensive individuals are hyperinsulinemic<sup>[34]</sup>; and approximately 75% of people with type 2 diabetes have hypertension.<sup>[35]</sup> Peritoneal fat, which is increased in the insulin resistance syndrome, produces excessive angiotensinogen.<sup>[36]</sup> This, along with high insulin levels stimulating the sympathetic nervous system<sup>[37]</sup> and increasing angiotensin II production,<sup>[38]</sup> results in a higher sensitivity of the cardiovascular system to the adverse trophic effects of the renin angiotensin aldosterone system (RAAS).<sup>[39,40]</sup> This latter effect is evidenced by the frequent occurrence of diffuse arterial disease and left ventricular hypertrophy in diabetic patients, even when the lipid and blood pressure levels are normal. Diabetic patients, in particular, benefit from blockade of the RAAS, with reduction of cardiovascular mortality up to 40% in large, randomized, controlled trials of ACE inhibitors and/or ARBs.<sup>[14,41]</sup>

## **Are Current Strategies to Control Diabetes Effective?**

The traditional management of type 2 diabetes has been ineffective in altering this dismal prognosis because efforts have focused solely on lowering glucose levels, which is only one manifestation of the insulin resistance syndrome. If the prognosis is to be improved, the underlying pathophysiologic defect, i.e. insulin resistance, must be addressed. When insulin sensitivity is improved either by non-pharmacological or pharmacological agents, the atherogenic manifestations of the insulin resistance syndrome: hypertension, dyslipidemia, inflammation, and hypercoagulability as well as glucose homeostasis will be improved.

## **Lifestyle Changes to Improve the Risk of Type 2 Diabetes**

Excess brown adipose tissue, particularly when deposited intra-abdominally, is closely related to the development and progression of insulin resistance and type 2 diabetes.<sup>[42]</sup> Weight loss in overweight or obese individuals is perhaps the most effective way to improve insulin sensitivity. A hypo-caloric diet (more calories burned than consumed on a daily basis) resulting in significant weight loss ( $\geq 5\%$ - $10\%$  of body weight) regardless of the diet utilized, will markedly improve the capacity for insulin release and the other manifestations of the metabolic syndrome.<sup>[43]</sup>

Low glycemic load, high fiber diet which contains adequate amounts of mono-unsaturated and omega-3 fats and lean protein can improve satiety and dietary thermo-genesis (basal metabolic rate) and decrease insulin resistance.<sup>[44,45]</sup> Non-fat dairy products, soy foods, and a modest alcohol intake (not more than 1 drink per day for women or 2 drinks per day for men) can also improve insulin sensitivity.<sup>[46-48]</sup>

Calorie-dense foods, especially in the form of highly processed carbohydrates (sugars and starches), have a disproportionate effect on insulin sensitivity and promote weight gain which further increases insulin resistance.<sup>[44]</sup> Nutrients that have also been associated with worsening insulin sensitivity include trans-fats and saturated fats.<sup>[46]</sup>

Exercise improves insulin sensitivity and lowers glucose levels both acutely and for up to 48 h after physical activity, as shown by a recent study of healthy subjects exercising for 30 min or more at least three times weekly.<sup>[49]</sup> Exercise also lowers triglyceride levels, raises high-density lipoprotein cholesterol levels, and increases the basal metabolic rate, which facilitates weight loss.<sup>[50]</sup> A recent trial demonstrated marked immediate improvements in triglyceride levels (-25%) and endothelial function (25%) following a single 90-min walk on a treadmill.<sup>[51]</sup> While insulin resistance is worsened by increased adipose tissue mass especially when this is visceral, it is improved by an increased skeletal muscle mass.<sup>[52]</sup> Strength training (e.g. weight lifting) has been shown to improve all of the manifestations of the metabolic syndrome since skeletal muscles account for almost 80% of insulin-stimulated glucose disposal.<sup>[53]</sup> Thus, increasing the utilization of glucose by either increasing muscle mass and/or increasing muscle sensitivity (i.e. aerobic exercise) is a highly effective means of improving glucose homeostasis.<sup>[49,52]</sup>

Studies have been initiated in the last decade to determine the feasibility and benefit of various strategies to prevent or delay the onset of type 2 diabetes ( [Table 2](#) ). In the Diabetes Prevention Program (DPP)<sup>[5]</sup>, subjects were randomized to one of three intervention groups, which included the intensive nutrition and exercise counseling ('lifestyle') group or either of two masked medication treatment groups: the biguanide metformin group or the placebo group. The latter interventions were combined with standard diet and exercise recommendations. After an average follow-up of 2.8 years, a 58% relative reduction in the progression to diabetes was observed in the lifestyle group, and a 31% relative reduction in the progression of diabetes was observed in the metformin group compared with control subjects.

In the Finnish Diabetes Prevention Study,<sup>[6]</sup> middle-aged obese subjects with impaired glucose tolerance (IGT) were randomized to receive either brief diet and exercise counseling (control group) or intensive individualized instruction on weight reduction, food intake, and guidance on increasing physical activity (intervention group). After an average follow-up of 3.2 years, there was a 58% relative reduction in the incidence of diabetes in the intervention group compared with the control group.

In the Da Qing Study,<sup>[7]</sup> men and women from health care clinics in the city of Da Qing, China, were screened with the oral glucose tolerance test (OGTT), and those with IGT were randomized by clinic to a control group or to one of three active treatment groups: diet only, exercise only, or diet plus exercise. Subjects were re-examined biannually, and after an average of 6 years follow-up, the diet, exercise, and diet-plus-exercise interventions were associated with 31%, 46%, and 42% reductions in risk of developing type 2 diabetes, respectively.

## **Medications to Reduce the Incidence of New-Onset Diabetes**

The incidence of developing diabetes has been reduced by several oral pharmacologic anti-diabetic agents ( [Table 2](#) ). The biguanide metformin reduced the risk of diabetes by 31% in the DPP.<sup>[5]</sup> In the Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOPNIDDM),<sup>[8]</sup> participants with IGT were randomized in a double-blind fashion to receive either the alpha-glucosidase inhibitor acarbose or a placebo. After a mean follow-up of 3.3 years, a 25% relative risk reduction in progression to diabetes, based on one OGTT, was observed in the acarbose-treated group compared with the placebo group. In the Troglitazone in Prevention of Diabetes (TRIPOD) study,<sup>[9]</sup> after a median followup of 30 months, troglitazone

treatment was associated with a 56% relative reduction in progression to diabetes as compared with placebo in Hispanic women with previous gestational diabetes.

Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS)<sup>[10]</sup> was the first study to demonstrate that an anti-obesity agent, orlistat (Xenical), was able to reduce the progression to diabetes in obese subjects as compared with lifestyle changes alone. In this study, obese subjects (body mass index  $\geq 30$  kg/m<sup>2</sup>) were randomized to receive orlistat or placebo. After 4 years of follow-up, orlistat reduced the risk of diabetes by 37% and was associated with significant and sustained reductions in cardiovascular risk factors such as arterial blood pressure and lipid levels as compared to placebo.

Additionally, multiple large prospective trials have reported an unexpected reduction in the development of new type 2 diabetes mellitus in patients treated with anti-hypertensive agents. These trials predominately utilized ACE inhibitors or ARBs and have consistently demonstrated reductions in the risk of new diabetes ranging from 2% to 87% ( [Table 3](#) ). Two of these trials, namely Candesartan in Heart Failure - Assessment of Reduction in Mortality and Morbidity (CHARM)<sup>[23]</sup> and Studies of Left Ventricular Dysfunction (SOLVD),<sup>[25]</sup> involved chronic heart failure patients. Heart failure is an insulin resistant state in which the development of diabetes is particularly associated with increased morbidity and mortality.<sup>[54]</sup>

The recently published Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial<sup>[26]</sup> studied the outcomes in hypertensive patients at increased cardiovascular risk. This study was a major randomized, double-blind controlled trial of RAAS blockers that included the development of new type 2 diabetes as a pre-specified endpoint. Patients (15 245), aged 50 years or older, were randomized to valsartan or amlodipine; hydrochlorothiazide was added to patients in either arm of the trial if blood pressure control was suboptimal with monotherapy. Valsartan reduced the incidence of new-onset diabetes by 23%. The VALUE investigators suggested a positive effect of this drug on long-term insulin sensitivity. A similar proportion of patients in both arms of the VALUE trial needed adjunctive diuretic and/or beta blocker therapy for blood pressure control, thus the reduction in new diabetes was not due to increased insulin resistance caused by other medications.

The International Verapamil-Trandolapril Study (INVEST) trialists<sup>[24]</sup> reported that in 16 176 non-diabetic, hypertensive patients with CHD, the incidence of new diabetes was significantly lower in the verapamil sustained release/trandolapril strategy (7%), compared with the atenolol/hydrochlorothiazide strategy (8.2%). Treatment with hydrochlorothiazide 25 mg daily was associated with new diabetes in both strategies, whereas increased exposure to the ACE inhibitor trandolapril in the verapamil sustained release strategy appeared to be associated with more protection from new diabetes than the atenolol/hydrochlorothiazide strategy.

The Intervention as a Goal in Hypertension Treatment (INSIGHT)<sup>[15]</sup> showed that, after almost 5 years, 5.4% of the non-diabetic, hypertensive patients randomized to the nifedipine gastrointestinal transport system developed new diabetes, compared to 7% of those assigned the thiazide diuretic co-amilofide (hydrochlorothiazide 25 mg plus amiloride 2.5 mg) with or without a beta-blocker.

Most recently, results from the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) were presented in the late-breaking clinical

trials session at the American College of Cardiology's 2005 meeting. Patients in the amlodipine/ perindopril arm of the study had a highly significant 32% reduction in the incidence of new-onset diabetes as compared to those in the atenolol/bendroflumethiazide arm after a mean follow-up of 5.4 years.<sup>[55]</sup>

Traditional beta-blockers worsen insulin sensitivity and increase the risk of developing new diabetes. Carvedilol, an alpha-beta blocker with anti-oxidant properties, however, has been shown to improve, rather than worsen, insulin sensitivity. In the large Carvedilol Or Metoprolol European Trial (COMET), 3029 patients were randomized to either carvedilol or metoprolol in the setting of heart failure. Carvedilol reduced newonset diabetes by approximately 22% in 4.8 years.<sup>[22]</sup> More recently, in the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial, 1235 patients with type 2 diabetes and hypertension were randomized to carvedilol or metoprolol. All patients were also receiving either an ACE inhibitor or an ARB. At 35 weeks, carvedilol resulted in better glycosylated hemoglobin levels with significantly improved insulin sensitivity as measured by the HOMA (homeostasis model assessment) technique. It also reduced the development of micro-albuminuria compared to metoprolol.<sup>[56]</sup>

These data from the above-mentioned trials appear consistent and suggest that the incidence of new-onset diabetes was lower in one randomly assigned treatment group (containing ACE inhibitors, ARBs, some calcium channel blockers and/or carvedilol) than the other (containing diuretics in high doses and/or traditional beta-blockers). All of these trials were prospective, randomized, and included patients with or at high risk of CHD, and the majority had less than optimal blood pressure control at baseline.

However, limitations to these trials do exist. These include the fact that the definition of 'diabetes' differed among them. In some of these trials, thiazide diuretics and/or beta-blockers were used in some patients assigned to agents blocking the effects of angiotensin II (ACE inhibitors or ARBs) or calcium antagonists. This probably minimized the differences observed in emergence of new diabetes between the treatment groups in these trials. The same or similar blood pressure reduction was not achieved in each of the treatment groups in all of the studies, which may have contributed to the disproportionate development of diabetes. In the second Swedish Trial in Old Patients with hypertension (STOP-2),<sup>[13]</sup> the Nordic Diltiazem Study (NORDIL),<sup>[16]</sup> the amlodipine arm of the Antihypertensive and Lipid- Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),<sup>[18]</sup> and The Study on Cognition and Prognosis in the Elderly (SCOPE),<sup>[20]</sup> the reduction in the incidence of new-onset diabetes was not statistically significant. Lastly, it must be emphasized that, except in VALUE<sup>[26]</sup> and the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE),<sup>[21]</sup> new-onset diabetes was not a pre-specified endpoint. Although the latter trial has shown an impressive 87% reduction in the incidence of diabetes with candesartan as compared to atenolol, this should be taken with reservation since it was a small study with a short follow-up period.

## **Potential Mechanisms of Action of the Antihypertensive Agents**

The mechanisms of action whereby these medications prevent type 2 diabetes are speculative.<sup>[25]</sup> ACE inhibitors not only block the conversion of angiotensin I to angiotensin II, but also increase bradykinin levels through inhibition of kininase II-mediated degradation.<sup>[57,58]</sup> These higher levels lead to increased production of

prostaglandins E<sub>1</sub> and E<sub>2</sub> and nitric oxide, which improve exercise-induced glucose metabolism<sup>[59]</sup> and muscle sensitivity to insulin,<sup>[60-62]</sup> resulting in enhanced insulin-mediated glucose uptake. Furthermore, the peripheral vasodilatory actions of ACE inhibitors and ARBs lead to an improvement in skeletal muscle blood flow, the primary target for insulin action and an important determinant of glucose uptake. This effectively increases the surface area for glucose exchange between the vascular bed and skeletal muscles. Clinical evidence supporting this effect has been provided by Morel and coworkers,<sup>[63]</sup> who have shown improved insulin sensitivity when enalapril was given for 12 weeks to 14 obese, hypertensive, and dyslipidemic patients.

The protection against new diabetes may in part be related to adipocyte function. Reducing angiotensin II levels with an ACE inhibitor or blocking the angiotensin II receptor with an ARB may promote differentiation of pre-adipocytes to mature adipocytes, which serve as a sump for fat.<sup>[64]</sup> ARBs and ACE inhibitors may favorably affect the pancreatic beta cell by increasing islet blood flow<sup>[65]</sup> and preserving beta cell function.<sup>[66]</sup>

Carvedilol is a combined alpha/beta-blocker. The 7% alpha-1 blockade is enough to improve insulin sensitivity. Studies indicate that the difference in insulin sensitivity between carvedilol and a first or second generation beta-blocker is equivalent to that seen with adding a thiazolidinedione at high dose.<sup>[22,56,67]</sup> Simultaneous alpha blockade likely causes vasodilation of the vascular bed in skeletal smooth muscles, which in turn results in improved insulin sensitivity by increasing the surface area for exchange of glucose.

Calcium channel blockers are metabolically neutral with respect to blood sugar control. However, some have been associated with a lower incidence of diabetes in a number of studies, as above. Further trials are needed to elucidate the role, if any, of these agents in diabetes prevention.

## Conclusions

Lifestyle modifications including 30 or more min of exercise on most or preferably all days of the week, optimal diet (minimizing processed carbohydrates, saturated and trans-fats, and calories), and weight loss are highly effective in preventing type 2 diabetes.

An ACE inhibitor or ARB is a logical first line antihypertensive agent in patients with impaired fasting glucose or the metabolic syndrome for multiple reasons, including the reduction in risk of progression to overt type 2 diabetes. Even in subjects without diabetes or the metabolic syndrome, blood pressure levels previously thought to be in the 'high-normal' range (120/80-139/89) are associated with an increased risk of cardiovascular events<sup>[68]</sup> and, because of this, these levels are now considered to be 'pre-hypertension', per the new seventh Joint National Committee (JNC 7) guidelines.<sup>[69]</sup> Some of the most widely used anti-hypertensives, particularly the traditional beta blockers such as propranolol, timolol, metoprolol and atenolol, and diuretics such as hydrochlorothiazide and chlorthalidone (in high doses), worsen insulin resistance and increase the risk of developing type 2 diabetes.<sup>[18]</sup>

Prospective trials that specifically address the role of ACE inhibitors and ARBs in diabetes prevention are underway, including DREAM (Diabetes REDuction Approaches

with ramipril and rosiglitazone Medications), NAVIGATOR (Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research), ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), and TRANSCEND (Telmisartan Randomized Assessment Study in aCE iNtolerant subjects with cardiovascular Disease).

Our knowledge of the early stages of metabolic derangements that portend the diagnosis of diabetes, the recent success of major intervention trials, and the observations from the above-mentioned studies with ACE inhibitors and ARBs, clearly show that individuals at high risk can be identified and diabetes delayed, if not prevented. The cost-effectiveness of intervention strategies is unclear, but the huge burden resulting from the complications of diabetes and the potential ancillary benefits of some of the interventions suggest that an effort to prevent diabetes is worthwhile.

**Table 1. Risk Factors for Type 2 Diabetes**

Medscape®	www.medscape.com
Age > 45 years	
Overweight (BMI > 25 kg/m <sup>2</sup> *)	
First-degree relative with diabetes	
Habitual physical inactivity	
Member of a high-risk ethnic population (e.g., African-American, Latino, Native America, Asian-American, Pacific islander)	
Previously identified IFG or IGT	
History of gestational diabetes or delivery of a baby weighing > 9 lb	
Hypertensive (> 140/90 mmHg)	
HDL cholesterol < 35 mg/dL or triglyceride level > 250 mg/dL	
Polycystic ovary syndrome	
History of vascular disease	
BMI = body mass index; IFG = impaired fasting glucose; IGT = impaired glucose tolerance *May not be correct for all ethnic groups	
Source: Curr Med Res Opin © 2005 Librapharm Limited	

**Table 2. Prevention of Type 2 Diabetes: Prospective, Randomized Controlled Trials in Persons With Impaired Glucose Tolerance (IGT)**



Trial	Number of patients	Follow-up (years)	Risk reduction measure	Reduction in new-onset
Diabetes Prevention Project (DPP) <sup>5</sup>	3234	2.8	Metformin, lifestyle change, troglitazone* <sup>11</sup>	31%, 58%
Finnish Diabetes Prevention Study <sup>6</sup>	522	3.2	Intensive lifestyle change	58%
Da Qing IGT and Diabetes Study <sup>7</sup>	577	6	Diet and/or exercise	31%–
STOP-NIDDM <sup>8</sup>	1400	3.9	Acarbose	25%
TRIPOD <sup>9</sup>	266†	2.5	Troglitazone	56%
XENDOS <sup>10</sup>	3304	4	Orlistat	37%

\*Due to concern regarding its liver toxicity, randomization to and use of troglitazone were discontinued

†Hispanic women with gestational diabetes mellitus

STOP-NIDDM: Study to Prevent NIDDM; TRIPOD: Troglitazone in the Prevention of Diabetes; XENDOS: Xenical Prevention of Diabetes in Obese Subjects

**Table 3. Reduction in the Incidence of New-Onset Diabetes According to Study and Drug Treatment**

Trial	Number of patients	Follow-up (years)*	Primary drugs
CAPPP <sup>12</sup>	10 985	6.1	Captopril vs. diuretic/beta-blocker
STOP-2 <sup>13</sup>	6614	5	Calcium antagonists vs. conventional drugs, ACE inhibitors vs. conventional drugs
HOPE <sup>14</sup>	9297	5	Ramipril vs. placebo
INSIGHT <sup>15</sup>	6321	4.3	Nifedipine GITS vs. co-amilofide
NORDIL <sup>16</sup>	10 916	4.5	Diltiazem vs. conventional drugs
LIFE <sup>17</sup>	9193	4.8	Losartan vs. atenolol
ALLHAT <sup>18</sup>	33 357	4.9	Amlodipine vs. chlorthalidone, lisinopril vs. chlorthalidone
ANBP2 <sup>19</sup>	5626	Median 4.1	Enalapril vs. hydrochlorothiazide
SCOPE <sup>20</sup>	4937	3.7	Candesartan vs. placebo
ALPINE <sup>21</sup>	392	1	Candesartan ± felodipine vs. atenolol ± hydrochlorothiazide
COMET <sup>22</sup>	3029	4.8	Carvedilol vs. metoprolol
CHARM <sup>23</sup>	7599	3.2	Candesartan vs. placebo
INVEST <sup>24</sup>	22 576	2.7	Verapamil ± trandolapril vs. atenolol ± hydrochlorothiazide
SOLVD <sup>25</sup>	4228	3.4	Enalapril vs. placebo
VALUE <sup>26</sup>	15 245	4.2	Valsartan vs. amlodipine
PEACE <sup>27</sup>	8290	Median 4.8	Trandolapril vs. placebo

\*Mean years of follow-up or as indicated

†p value not significant

CAPPP: Captopril Prevention Project; STOP-2: The second Swedish Trial in Old Patients with hypertension; HOPE: Heart Evaluation; INSIGHT: Intervention as a Goal in Hypertension Treatment; NORDIL: Nordic Diltiazem Study; LIFE: Losartan Intervention Endpoint Reduction in hypertension study; ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack; second Australian National Blood Pressure study; SCOPE: The Study on Cognition and Prognosis in the Elderly; ALPINE: Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation; COMET: Carvedilol Or Metoprolol European Trial; in Heart Failure – Assessment of Reduction in Mortality and Morbidity; INVEST: The International Verapamil–Trandolapril Studies Of Left Ventricular Dysfunction; VALUE: Valsartan Antihypertensive Long-term Use Evaluation; PEACE: Prevention of Angiotensin Converting Enzyme Inhibition Trial

Source: Curr Med Res Opin

## References

1. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998;21:1414-31
2. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2005;28:S4-S36
3. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 1999;104:787-94
4. Despres JP, Lamarche B, Mauriege P, et al. Hyperinsulinemia as an independent risk factor for ischemic heart disease. *New Engl J Med* 1996;334:952-7
5. Knowler WC, Barrett-Connor E, Fowler SE, et al., Diabetes Prevention

- Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New Engl J Med* 2002;346:393-403
6. Tuomilehto J, Lindstrom J, Eriksson JG, et al., Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New Engl J Med* 2001;344:1343-50
  7. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care* 1997;20:537-44
  8. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002;359:2072-7
  9. Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 2002;51:2796-803
  10. Scheen AJ. Info-congress. Prevention of type 2 diabetes in obese patients: first results with orlistat in the XENDOS study. *Rev Med Liege* 2002;57:617-21
  11. Knowler WC, Hamman RF, Edelstein SL et al. Prevention of type 2 diabetes with troglitazone in the diabetes prevention program. *Diabetes* 2005; 54:1150-6.
  12. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999;353:611-6
  13. Hansson L. Results of the STOP-hypertension-2 trial. *Blood Press Suppl* 2000;2:17-20
  14. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients [The Heart Outcomes Prevention Evaluation Study Investigators]. *New Engl J Med* 2000;342:145-53
  15. Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: intervention as a goal in hypertension treatment (INSIGHT). *Lancet* 2000;356:366-72
  16. Hansson L, Hedner T, Lund-Johansen P, et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet*. 2000;356:359-65.
  17. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;359:995-1003
  18. ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *J Am Med Assoc* 2002;288:2981-97
  19. Reid CM, Johnston, C.I., Ryan P., Willson K., Wing, L.M. Diabetes and cardiovascular outcomes in elderly subjects treated with ACE-inhibitors or diuretics: findings from the 2nd Australian National Blood Pressure Study [abstract]. *Am J Hypertens* 2003;16
  20. Lithell H, Hansson L, Skoog I, et al. The Study on Cognition and Prognosis in

- the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* 2003;21:875-86
21. Lindholm LH, Persson M, Alaupovic P, Carlberg B, Svensson A, Samuelsson O. Metabolic outcome during 1 year in newly detected hypertensives: results of the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE study). *J Hypertens* 2003;21:1563-74
  22. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* 2003;362:7-13
  23. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003;362:759-66
  24. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *J Am Med Assoc* 2003;290:2805-16
  25. Vermes E, Ducharme A, Bourassa MG, Lessard M, White M, Tardif JC. Enalapril reduces the incidence of diabetes in patients with chronic heart failure: insight from the Studies Of Left Ventricular Dysfunction (SOLVD). *Circulation* 2003;107: 1291-6
  26. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004;363:2022-31
  27. Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *New Engl J Med* 2004;351:2058-68
  28. Narayan KM, Boyle JP, Thompson TJ, Sorensen SW, Williamson DF. Lifetime risk for diabetes mellitus in the United States. *J Am Med Assoc* 2003;290:1884-90
  29. Grundy SM, Cleeman JI, Merz CN, et al., Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *J Am Coll Cardiol* 2004;44:720-32
  30. Nakanishi N, Takatorige T, Fukuda H, et al. Components of the metabolic syndrome as predictors of cardiovascular disease and type 2 diabetes in middle-aged Japanese men. *Diabetes Res Clin Pract.* 2004;64:59-70.
  31. Sattar N, Gaw A, Scherbakova O, et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation.* 2003;108:414-9.
  32. Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the United States. *J Am Med Assoc* 2001;286:1195-200
  33. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *J Am Med Assoc* 2002;287:356-9
  34. Zavaroni I, Mazza S, Dall'Aglio E, Gasparini P, Passeri M, Reaven GM. Prevalence of hyperinsulinaemia in patients with high blood pressure. *J Intern Med* 1992;231:235-40
  35. Kaplan NM. Treating hypertension in the diabetic patient. *Clin Diabetes* 1987;5:25-34
  36. Frederich Jr RC, Kahn BB, Peach MJ, Flier JS. Tissue-specific nutritional

- regulation of angiotensinogen in adipose tissue. *Hypertension* 1992;19:339-44
37. Watanabe K, Sekiya M, Tsuruoka T, et al. Relationship between insulin resistance and cardiac sympathetic nervous function in essential hypertension. *J Hypertens* 1999;17:1161-8
  38. Tuck ML, Bounoua F, Eslami P, Nyby MD, Eggena P, Corry DB. Insulin stimulates endogenous angiotensin II production via a mitogen-activated protein kinase pathway in vascular smooth muscle cells. *J Hypertens* 2004;22:1779-85
  39. O'Keefe JH, Wetzel M, Moe RR, Bronsnahan K, Lavie CJ. Should an angiotensin-converting enzyme inhibitor be standard therapy for patients with atherosclerotic disease? *J Am Coll Cardiol* 2001;37:1-8
  40. Rocchini AP, Moorehead C, DeRemer S, Goodfriend TL, Ball DL. Hyperinsulinemia and the aldosterone and pressor responses to angiotensin II. *Hypertension* 1990;15:861-6
  41. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253-9
  42. Valverde AM, Benito M, Lorenzo M. The brown adipose cell: a model for understanding the molecular mechanisms of insulin resistance. *Acta Physiol Scand* 2005;183:59-73
  43. Yoshida Y, Hashimoto N, Tokuyama Y, et al. Effects of weight loss in obese subjects with normal fasting plasma glucose or impaired glucose tolerance on insulin release and insulin resistance according to a minimal model analysis. *Metabolism* 2004;53:1095-100
  44. Brand-Miller JC. Postprandial glycemia, glycemic index, and the prevention of type 2 diabetes. *Am J Clin Nutr* 2004;80:243-4
  45. Esposito K, Marfella R, Ciotola M, et al. Effect of a Mediterranean style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *J Am Med Assoc* 2004;292:1440-6
  46. Laaksonen DE, Lakka TA, Lakka HM, et al. Serum fatty acid composition predicts development of impaired fasting glycaemia and diabetes in middle-aged men. *Diabetic Med* 2002;19:456-64
  47. Lavigne C, Marette A, Jacques H. Cod and soy proteins compared with casein improve glucose tolerance and insulin sensitivity in rats. *Am J Physiol Endocrinol Metab* 2000;278:E491-E500
  48. Thamer C, Haap M, Fritsche A, Haering H, Stumvoll M. Relationship between moderate alcohol consumption and adiponectin and insulin sensitivity in a large heterogeneous population. *Diabetes Care* 2004;27:1240
  49. Boule NG, Weisnagel SJ, Lakka TA, et al. Effects of exercise training on glucose homeostasis: the HERITAGE Family Study. *Diabetes Care* 2005;28:108-14
  50. Kraus WE, Houmard JA, Duscha BD, et al. Effects of the amount and intensity of exercise on plasma lipoproteins. *New Engl J Med* 2002;347:1483-92
  51. Gill JM, Al-Mamari A, Ferrell WR, et al. Effects of prior moderate exercise on postprandial metabolism and vascular function in lean and centrally obese men. *J Am Coll Cardiol* 2004;44:2375-82
  52. Kim CS, Nam JY, Park JS, et al. The correlation between insulin resistance and the visceral fat to skeletal muscle ratio in middle-aged women. *Yonsei Med J* 2004;45:469-78
  53. Dunstan DW, Daly RM, Owen N, et al. High-intensity resistance training

- improves glycemic control in older patients with type 2 diabetes. *Diabetes Care* 2002;25:1729-36
54. Swan JW, Anker SD, Walton C, et al. Insulin resistance in chronic heart failure: relation to severity and etiology of heart failure. *J Am Coll Cardiol* 1997;30:527-32
  55. Sever PS DB, Poulter NR, Wedel H. The Anglo-Scandinavian Cardiac Outcomes Trial: morbidity-mortality outcomes in the blood pressure lowering arm of the trial (ASCOT-BPLA). American College of Cardiology Annual Scientific Session 2005, March 6-9, Orlando, Florida. Late Breaking Clinical Trials 2
  56. Bakris GL, Fonseca V, Katholi RE, et al., GEMINI Investigators. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *J Am Med Assoc* 2004;292:2227-36
  57. Uehara M, Kishikawa H, Isami S, et al. Effect on insulin sensitivity of angiotensin converting enzyme inhibitors with or without a sulphhydryl group: bradykinin may improve insulin resistance in dogs and humans. *Diabetologia* 1994;37:300-7
  58. Yang HY, Erdos EG, Levin Y. A dipeptidyl carboxypeptidase that converts angiotensin I and inactivates bradykinin. *Biochim Biophys Acta* 1970;214:374-6
  59. Balon TW, Nadler JL. Evidence that nitric oxide increases glucose transport in skeletal muscle. *J Appl Physiol* 1997;82:359-63
  60. Leighton B, Budohoski L, Lozeman FJ, Challiss RA, Newsholme EA. The effect of prostaglandins E1, E2 and F2 alpha and indomethacin on the sensitivity of glycolysis and glycogen synthesis to insulin in stripped soleus muscles of the rat. *Biochem J* 1985;227:337-40
  61. Fryer LG, Hajduch E, Rencurel F, et al. Activation of glucose transport by AMP-activated protein kinase via stimulation of nitric oxide synthase. *Diabetes* 2000;49:1978-85
  62. Henriksen EJ, Jacob S, Kinnick TR, Youngblood EB, Schmit MB, Dietze GJ. ACE inhibition and glucose transport in insulinresistant muscle: roles of bradykinin and nitric oxide. *Am J Physiol* 1999;277:R332-6
  63. Morel Y, Gadiant A, Keller U, Vadas L, Golay A. Insulin sensitivity in obese hypertensive dyslipidemic patients treated with enalapril or atenolol. *J Cardiovasc Pharmacol* 1995;26: 306-11
  64. Sharma AM, Janke J, Gorzelniak K, Engeli S, Luft FC. Angiotensin blockade prevents type 2 diabetes by formation of fat cells. *Hypertension* 2002;40:609-11
  65. Carlsson PO, Berne C, Jansson L. Angiotensin II and the endocrine pancreas: effects on islet blood flow and insulin secretion in rats. *Diabetologia* 1998;41:127-33
  66. Santoro D, Natali A, Palombo C, et al. Effects of chronic angiotensin converting enzyme inhibition on glucose tolerance and insulin sensitivity in essential hypertension. *Hypertension* 1992;20:181-91
  67. Jacob S, Balletshofer B, Henriksen EJ, et al. Beta-blocking agents in patients with insulin resistance: effects of vasodilating betablockers. *Blood Press* 1999;8:261-8
  68. Vasan RS, Larson MG, Leip EP, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. *New Engl J Med* 2001;345:1291-7
  69. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood

Pressure. Hypertension 2003;42:1206-52