Effects of hypoglycemic agents on mortality and major cardiovascular outcomes in patients with type 2 diabetes mellitus: a narrative review [88]

ABSTRACT

Type 2 diabetes mellitus acts as a risk factor for cardiovascular disease. It has been hypothesized that control of plasma glucose levels would reduce cardiovascular disease in type 2 diabetic patients – thus lowering parameters such as mortality rate, myocardial infarction or stroke. A narrative review was carried out looking at data on mortality and cardiovascular disease outcomes, including myocardial infarction and stroke, associated with hypoglycemic therapy in type 2 diabetic patients, starting with the University Group Diabetes Trial (1970-1978) and ending with the Veterans Affairs Diabetes Trial (2009). The data reviewed in the present text fail to confirm the hypothesis presented above. No consistent relation between lowering plasma glucose and favorable effects either on mortality rate or on major cardiovascular disease has been clearly shown to exist. However, there are interesting data concerning drugs that lower plasma insulin levels, particularly metformin, but also, to a certain degree, pioglitazone. Also of interest are data on a possible legacy effect observed in the long-
term follow-up of patients previously under intensive plasma glucose control. Consistent evidence in favor of lowering glycated hemoglobin levels to values under 7% also seems to be lacking at present, at least concerning mortality and cardiovascular outcomes.

For the time being, it can be argued that efforts should be centered on interventions with clear evidence of benefit, such as treatment of hypertension or excessive weight, as well as the use of statins.

**Key words**
Diabetes mellitus; Myocardial infarction; Stroke; Mortality; Outcome.

**INTRODUCTION**

Diabetes mellitus is a disease characterized by chronic hyperglycemia. Type 1 diabetes patients have insulin deficiency, due to decreased insulin production by the pancreas. Type 2 diabetes patients, on the other hand, are frequently either overweight or obese, and the main problem may often be resistance to the effects of insulin, rather than lack of the hormone.

Diabetes appears to act as a risk factor for cardiovascular disease (CVD), including coronary heart disease, cerebrovascular disease, and peripheral artery disease, as well as retinopathy, nephropathy, and neuropathy. In the Framingham Heart Study, cardiovascular disease was twice as common in men and three times as common in women among diabetic as among nondiabetic individuals. Diabetes is one of the main causes of end-stage renal disease, a disease that is now of epidemic proportions. Cardiovascular death accounts for a significant proportion of all deaths among those with type 2 diabetes. Haffner et al., studying the 7-year incidence of myocardial infarction in a Finnish population, found that “diabetic patients without previous myocardial infarction have as high a risk of myocardial infarction as nondiabetic patients with previous myocardial infarction.” This higher cardiovascular risk may be related in part to a high prevalence of other risk factors, such as smoking, elevated blood pressure and dyslipidemia. In the Multiple Risk Factor Intervention Trial, cardiovascular mortality was three times higher in diabetic than in nondiabetic men. Moreover, Stamler et al. found that “For diabetic men with higher values for each risk factor and their combinations, absolute risk of CVD death increased more

**Palavra-chave:**
Diabetes mellitus; Enfarte do miocárdio; Acidente vascular cerebral; Mortalidade.
steeply than for nondiabetic men”\(^4\).

Current medical care of type 2 diabetes includes a series of lifestyle and pharmacological interventions, among them drugs aimed at controlling hyperglycemia. It has been hypothesized that since patients with high plasma glucose have an increased incidence and prevalence of cardiovascular disease, control of plasma glucose levels would reduce cardiovascular disease in these patients. This hypothesis, however, is in need of empirical confirmation. There could be one or more confounders, as in the classic example of the relationship between carrying matches and developing lung cancer\(^5\). Plasma glucose molecules could be the matches in this story – the wrong surrogate endpoint, according to one perspective\(^6\).

The aim of the present narrative review was to analyze existing data on the effects of hypoglycemic agents on cardiovascular outcomes and mortality, in patients with type 2 diabetes mellitus. The selection of the research papers to be included in this review took into consideration the number of patients studied (studies with less than one hundred patients not being considered) and the duration of the study (interventions with a duration up to one year not being considered), as well as the correspondence between each study’s objectives and the objective of the present report. Reports on drugs for which further development was discontinued and not currently on the market were also not considered (e.g. reports on muraglitazar). A preliminary evaluation of selected papers led the authors to conclude that they were sufficiently heterogeneous to justify an individual description of each study.

The present report was not funded by any interested party, either industry or governmental, and the decision to carry out this review was taken exclusively by the authors.

2. MAJOR CLINICAL TRIALS STUDYING THE EFFECTS ON MORTALITY OF HYPOGLYCEMIC DRUGS


The University Group Diabetes Program (UGDP) was a randomized prospective clinical trial, the main findings of which were published in 1970-1978\(^7\). The study was carried out from 1961 to 1975 (with a minimum of 9 years from randomization to the end of the study). The main inclusion criteria were: “diabetes diagnosis within 12 months”\(^7\); “diagnosis confirmed by glucose tolerance test”\(^7\); “ketosis free on diet alone”\(^7\); and “life expectancy of at least five years”\(^7\).

Regarding the 1978 report – the UGDP insulin study\(^9\) – 619 patients were recruited and randomly allocated to one of three treatment groups: 205 in placebo (diet alone), 210 in insulin standard, and 204 in insulin variable. Patients assigned to the insulin variable group were given the amount of insulin required to lower their blood glucose levels to pre-specified targets. Patients assigned to the insulin standard group were given an amount of insulin based on an estimate of the patient’s body surface. In the insulin variable group, the aim was a fasting glucose value <110 mg/dl or a one-hour fasting glucose value <210 mg/dl. Three aggregate endpoints were chosen: cardiovascular-related mortality; non-cardiovascular-related mortality; and all-cause mortality. Other cardiovascular events were also monitored, such as first occurrence of: significant ECG abnormality; use of digitalis; hospitalization for heart disease; hypertension; angina pectoris; amputation of all or part of either lower limb; arterial calcification; and intermittent claudication. Some of the major results of the UGDP insulin study are shown in Table I. No relation between lower glucose levels and better mortality/cardiovascular outcomes was seen.

A previous report on mortality within the above three treatment groups and a fourth treatment group under tolbutamide therapy (1.5 g per day) was issued in 1970\(^7\). A total of 204 patients were assigned to tolbutamide therapy. Tolbutamide-treated patients had a higher cardiovascular mortality rate than the placebo group, a finding that led to a discontinuation of tolbutamide therapy in the UGDP (Table II). Mean values for fasting plasma glucose at the end of the nineteenth follow-up examination were lower than baseline values in the insulin variable group, and higher than baseline values in the other three groups (11.6% for placebo,
Table I. Insulin vs. placebo study from the University Group Diabetes Program (1978)

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo (n=205)</th>
<th>Insulin Standard (n=210)</th>
<th>Insulin Variable (n=204)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean FPG difference from baseline at 8.75 years</td>
<td>+22.3%</td>
<td>+15.9%</td>
<td>-13.5%</td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>1</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Sudden death</td>
<td>11</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Death from all cardiovascular causes</td>
<td>29</td>
<td>27 (0.81)</td>
<td>29 (1.00)</td>
</tr>
<tr>
<td>Death from all causes</td>
<td>54</td>
<td>48 (0.48)</td>
<td>49 (0.67)</td>
</tr>
<tr>
<td>Reported hypoglycemic episodes</td>
<td>0</td>
<td>22</td>
<td>80</td>
</tr>
<tr>
<td>Hypertension (SBP ≥ 160 mmHg)</td>
<td>50.0%</td>
<td>54.7% (0.52)</td>
<td>55.6% (0.42)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>19.6%</td>
<td>15.5% (0.37)</td>
<td>16.6% (0.54)</td>
</tr>
</tbody>
</table>

FPG: fasting plasma glucose; SBP: systolic blood pressure; DBP: diastolic blood pressure. In brackets, p vs. placebo. Data adapted from (9).

Table II. Mortality results from the University Group Diabetes Program - tolbutamide data (1970).

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo (n=205)</th>
<th>Insulin standard (n=210)</th>
<th>Insulin Variable (n=204)</th>
<th>Tolbutamide (n=204)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from all cardiovascular causes</td>
<td>10</td>
<td>13</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>Death from all causes</td>
<td>21</td>
<td>20</td>
<td>18</td>
<td>30</td>
</tr>
</tbody>
</table>

Data adapted from (7).

7.1% for tolbutamide and 3.3% for insulin standard.

A fifth treatment group with phenformin (100 mg/day) was started about 18 months after the start of the other 4 groups of patients, and only in 6 clinics. A report on phenformin therapy was published in 1975 (8). A total of 204 patients were assigned to phenformin therapy. The results obtained in this group were compared to results in patients seen in the same clinics and in different treatment arms of the study – placebo, 64 patients; insulin standard, 68 patients; insulin variable, 65 patients. A higher percentage of patients in the phenformin group died than in the other groups (Table III). The authors stated that “there was an indication that phenformin had adverse effects compared to the effects of insulin and diet or diet alone” (8). Mean values for fasting plasma glucose at the end of the twenty-third follow-up examination were lower than baseline values in all groups: -17.1% in the insulin variable group, -0.6% for placebo, -8.9% for phenformin and -10.9% for insulin standard. One fatal and two nonfatal cases of lactic acidosis were seen with phenformin therapy. Increased blood pressure levels and heart rate were also seen with phenformin therapy.

2.2. Veterans Affairs Diabetes Feasibility Trial (1993)

The Veterans Affairs Diabetes Feasibility Trial (VACSDM – Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes) was a randomized controlled trial conducted at five Veterans Affairs (VA) medical centers (10). The study was carried out from May 1990 to April 1993, with a mean follow-up of 27 months (10). Inclusion criteria were: men with non-insulin dependent diabetes, aged 40 to 69 years, who had hemoglobin A1c (HbA1c) levels of over 6.55% while receiving sulfonylurea or insulin therapy. The main exclusion criteria were: more than one preexisting
myocardial infarction, severe congestive heart failure (New York Heart Association functional class III or IV), amputation due to gangrene, albuminuria greater than 500 mg/d, a serum creatinine level greater than 1.6 mg/dl, and symptomatic neuropathy.

A total of 289 patients were screened and 153 patients were recruited and randomized to treatment, either with intensive glucose control (defined as the use of glucose-lowering drugs - stepped plan starting with one insulin injection, progressing to one insulin injection plus gliclazide, to two insulin injections, and to three or more insulin injections – as required to achieve glycated hemoglobin between 4.0% and 6.0%; n=75) or standard glucose control (one insulin injection per day; n=78).

The primary study outcomes were myocardial infarction, congestive heart failure, stroke, amputation for ischemic gangrene, cardiovascular mortality, angina or documented coronary disease, angioplasty or bypass graft surgery, transient ischemic attacks, new claudication and ischemic ulcers. Some of the main results are shown in (Table IV). A different mean HbA1c was seen when the two arms of the study were compared. This finding, however, was not accompanied by any significant difference in cardiovascular outcomes \(^{(10)}\). Severe hypoglycemia was seen with a non-significantly different incidence in both arms; mild and moderate hypoglycemia, however, was more common in the intensive treatment group.

### Table III. Mortality results from the University Group Diabetes Program - phenformin data (1975).

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=64)</th>
<th>Insulin standard (n=68)</th>
<th>Insulin Variable (n=65)</th>
<th>Tolbutamide (n=204)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from all cardiovascular causes</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>Death from all causes</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>34</td>
</tr>
</tbody>
</table>

Data adapted from \(^{(8)}\).

### Table IV. Major results from the Veterans Affairs Diabetes Feasibility Trial (1993)

<table>
<thead>
<tr>
<th></th>
<th>Standard treatment (n=78)</th>
<th>Intensive treatment (n=75)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with cardiovascular events</td>
<td>16</td>
<td>24</td>
<td>0.10</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>26</td>
<td>35</td>
<td>–</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>Deaths</td>
<td>5</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>Cardiovascular deaths</td>
<td>3</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>Mean % HbA1c at the end of the study (baseline 9.8%)</td>
<td>9.2</td>
<td>7.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HbA1c: glycated hemoglobin. Data adapted from \(^{(10)}\).

were referred by general practitioners to 23 participating hospitals. Patients with newly diagnosed diabetes with fasting plasma glucose (FPG) greater than 6 mmol/l were included in the study. Patients with any of the following criteria were excluded: *ketonuria more than 3
mmol/l; serum creatinine greater than 175 mmol/l; myocardial infarction in the previous year; current angina or heart failure; more than one major vascular event; retinopathy requiring laser treatment; malignant hypertension; uncorrected endocrine disorder” (11); “occupation that precluded insulin therapy” (11); “severe concurrent illness that would limit life or require extensive systemic treatment” (11). A total of 7616 patients were referred and 5102 were recruited (58% male, aged 25-65 years). After an initial 3 months of diet-only treatment, 4209 patients with FPG 6.1-15 mmol/l were stratified (by ideal bodyweight). Non-overweight patients were randomly assigned intensive treatment with insulin (30%), intensive treatment with sulfonylurea (40%; chlorpropamide, glibenclamide, or glipizide), or conventional treatment with diet (30%). Overweight patients were randomly assigned treatment with the additional possibility of metformin.

In the conventional treatment arm, patients received dietary advice aiming at maintaining FPG below 15 mmol/l, without symptoms of hyperglycemia. If marked hyperglycemia (FPG >15 mmol/l) or symptoms occurred, patients were secondarily randomized to treatment with sulfonylurea or insulin therapy, with the additional option of metformin in overweight patients. In the intensive treatment arm, the aim was FPG less than 6 mmol/l.

Three aggregate endpoints were chosen: any diabetes-related endpoint (“sudden death, death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycaemia or hypoglycaemia, and sudden death” (11); all-cause mortality. Some of the main results are shown in (Table V). A diabetes-related endpoint occurred in 438/1138 patients in the conventional treatment group, compared to 963/2729 patients in the intensive treatment group (relative risk of 0.88, 95% confidence interval [CI] 0.79-0.99) (11). No relation between lower glucose levels and better mortality/cardiovascular outcomes was seen.

### 2.4. UKPDS 34 (1998)

UKPDS 34 reports on two randomized controlled trials, in which metformin was a therapeutic option, the main findings of which were published in 1998 (5). These trials were carried out from 1977 to 1997 in conjunction with other UKPDS studies, and their inclusion and exclusion criteria have already been described (in section 2.3). After an initial 3 months of diet-only treatment, 4209 patients with FPG 6.1-15 mmol/l were recruited and stratified by ideal bodyweight.

In the trial of overweight (defined as ≥120% ideal body weight), diet-treated patients (46% male, with a mean age of 53 years), 411 overweight patients were assigned conventional

<table>
<thead>
<tr>
<th>Table V. Some major findings of UKPDS 33.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional treatment</strong></td>
</tr>
<tr>
<td><strong>Target FPG &lt;15 mmol/l</strong></td>
</tr>
<tr>
<td><strong>(n=1138)</strong></td>
</tr>
<tr>
<td>HbA1c at 10 years</td>
</tr>
<tr>
<td>All-cause mortality</td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Fatal stroke</td>
</tr>
</tbody>
</table>

RR: relative risk; CI: confidence interval; FPG: fasting plasma glucose * significantly different from intensive treatment group. Data adapted from (11).
treatment and were compared to 342 overweight patients assigned intensive treatment with metformin. A secondary analysis compared outcomes between the 342 overweight patients allocated intensive therapy with metformin and 951 overweight patients allocated intensive therapy with chlorpropamide (n=265), glibenclamide (n=277) or insulin (n=409).

In a supplementary randomized controlled trial, 537 non-overweight and overweight sulfonylurea-treated patients (60% male, with a mean age of 59 years), who had not reached the target FPG (<6 mmol/l), and had FPG of 6.1 to 15.0 mmol/l, were randomly assigned early addition of metformin to current treatment (n=269) or continued sulfonylurea alone (n=268). If those allocated sulfonylurea alone later developed hyperglycemia, metformin was added. If hyperglycemia persisted, oral therapy was stopped and changed to insulin therapy.

In both trials, the primary endpoints were any diabetes-related clinical endpoint (as defined above), diabetes-related death, and all-cause mortality. A combined analysis of both trials was conducted to evaluate the impact of metformin on the primary endpoints selected. Some of the main results are shown in Tables VI and VII. Metformin therapy was associated with lower mortality and lower incidence of myocardial infarction (Table VI). On the other hand, higher mortality was seen with sulfonylurea/metformin combination therapy (Table VII).

2.5. UKPDS 80 (2008)

A 10-year, post-interventional follow-up of the UKPDS survivor cohort was carried out from 1997 to 2007 to observe the long-term impact of the interventions. A total of 3277 (79%) of the 4209 patients who underwent randomization in the original UKPDS entered post-trial monitoring. For the first 5 years of follow-up, patients attended annual UKPDS clinics for collection of outcome data, measurements of blood pressure and biochemical tests. In years 6 to 10, questionnaires were used to follow patients remotely. Patients were advised to maintain glycemia and blood pressure as low as possible, but no attempt was made to continue their previously randomized therapies.

The UKPDS clinical outcomes were any diabetes-related endpoint, diabetes-related death, death from any cause, myocardial infarction, stroke, peripheral vascular disease and microvascular disease.

Of the original 1138 patients who received conventional therapy, 370 completed post-trial monitoring; for the sulfonylurea/insulin intensive therapy group, the corresponding numbers were 2729/1010 and for the metformin group, the numbers were 342/136.

Some major results are shown in Table VIII. A decrease in mortality and myocardial infarction was seen in the intensive therapy group in 10-year post-trial follow-up, both in the sulfonylurea-insulin group and in the metformin group. After one year of follow-up, HbA1c levels were similar in the intensive and conventional therapy groups.

2.6. ACCORD (2008)

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial was a randomized controlled trial conducted at 77 clinical centers across the United States and Canada. The study was carried out from January 2001 to February 2008 (with a mean follow-up of 3.5 years). The inclusion criteria were: type 2 diabetes patients with a glycated hemoglobin level of 7.5% or more, either between the ages of 40 and 79 years with cardiovascular disease, or between the ages of 55 and 79 with “anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease (dyslipidemia, hypertension, current smoker or obesity)”.

Exclusion criteria included “frequent or recent serious hypoglycemic events, unwillingness to do home glucose monitoring or inject insulin, a body-mass index >45, serum creatinine level >1.5 mg/dl, or other serious illness.”

A total of 10,251 patients (aged 62.2±6.8 years) were recruited and randomized to treatment either with intensive glucose control (defined as the use of glucose-lowering drugs as required to achieve glycated hemoglobin <6.0%; n=5128) or standard glucose control (with target glycated hemoglobin levels
Table VI. Some major findings of the UKPDS 34 overweight patients study.

<table>
<thead>
<tr>
<th></th>
<th>Conventional treatment (diet)</th>
<th>Intensive treatment with metformin</th>
<th>RR for metformin treatment (95% CI)</th>
<th>Other intensive treatments - chlorpropamide, glibenclamide, insulin (p vs* metformin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target FPG &lt;15mmol/l</td>
<td>n=41</td>
<td>n=342</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c at 10 years</td>
<td>8.0*</td>
<td>7.4</td>
<td>0.68 (0.53-0.87)</td>
<td>350 (0.0034)</td>
</tr>
<tr>
<td>Any diabetes-related endpoint</td>
<td>160</td>
<td>96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>89</td>
<td>50</td>
<td>0.64 (0.45-0.91)</td>
<td>190 (0.021)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>73</td>
<td>39</td>
<td>0.61 (0.41-0.91)</td>
<td>139 (0.12)</td>
</tr>
<tr>
<td>Stroke</td>
<td>23</td>
<td>12</td>
<td>0.59 (0.29-1.16)</td>
<td>60 (0.032)</td>
</tr>
</tbody>
</table>

RR: relative risk. CI: confidence interval. FPG: fasting plasma glucose. *: significantly different from intensive treatment group. Data adapted from (12).

Table VII. Some major findings of the UKPDS 34 non-overweight and overweight patients study.

<table>
<thead>
<tr>
<th></th>
<th>Sulfonylurea treatment</th>
<th>Sulfonylurea plus metformin treatment</th>
<th>RR for treatment with sulfonylurea plus metformin (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=269</td>
<td></td>
<td>n=268</td>
<td></td>
</tr>
<tr>
<td>HbA1c at 4 years</td>
<td>8.2</td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>Any diabetes-related endpoint</td>
<td>82</td>
<td>81</td>
<td>1.04 (0.77-1.42)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>31</td>
<td>47</td>
<td>1.60 (1.02-2.52)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>31</td>
<td>33</td>
<td>1.09 (0.67-1.78)</td>
</tr>
<tr>
<td>Stroke</td>
<td>13</td>
<td>15</td>
<td>1.21 (0.58-2.65)</td>
</tr>
</tbody>
</table>

RR: relative risk. CI: confidence interval. Data adapted from (13).

Table VIII. Some major findings of the UKPDS 80 Follow-up Study.

<table>
<thead>
<tr>
<th></th>
<th>Sulfonylurea insulin group</th>
<th>Intensive therapy</th>
<th>Conventional therapy</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=2729</td>
<td></td>
<td>n=1138</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>1162</td>
<td>537*</td>
<td>0.87 (0.79-0.96)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>673</td>
<td>319*</td>
<td>0.85 (0.74-0.97)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>260</td>
<td>116</td>
<td>0.91 (0.73-1.13)</td>
<td></td>
</tr>
<tr>
<td>Metformin group</td>
<td>n=542</td>
<td>n=411</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>152</td>
<td>217*</td>
<td>0.73 (0.59-0.89)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>31</td>
<td>126*</td>
<td>0.67 (0.51-0.89)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>34</td>
<td>42</td>
<td>0.80 (0.50-1.27)</td>
<td></td>
</tr>
</tbody>
</table>

*: p<0.05 vs. intensive therapy group. RR: risk ratio for intensive therapy regimen (95% CI). Data adapted from (13).

between 7.0% and 7.9%; n=5123). The authors stated that “therapeutic regimens were individualized at the discretion of the investigators and patients on the basis of study-group assignment and the response to therapy”. The primary study outcome was the first occurrence of nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes (“death from myocardial infarction, heart failure, arrhythmia, invasive cardiovascular interventions, cardiovascular causes after noncardiovascular surgery, stroke, unexpected death presumed to be from ischemic cardiovascular disease, and death from other vascular diseases”). Death from any cause was a secondary outcome.
The intensive therapy arm of this study was discontinued 17 months before the scheduled end of the study due to the finding of higher mortality in this group (after a mean follow-up of 3.5 years). Patients in the intensive therapy group had “a greater exposure to drugs from every class”\(^{(14)}\); as an example, rosiglitazone was used by 91.2% of patients in the intensive therapy group, compared to 57.5% of patients in the standard therapy group.

Some of the main results are shown in Table IX. A higher mortality rate was seen in the intensive therapy group, as well as higher cardiovascular mortality. Mean HbA1c at the end of the study was 6.4% in the intensive therapy group, compared to 7.5% in the standard therapy group.

### 2.7. ADVANCE (2008)

The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) Trial was a randomized controlled trial conducted at 215 centers in 20 countries in North America, Europe, Australasia and Asia. Its main findings were published in 2008\(^{(15)}\). The study was carried out from June 2001 to January 2008 (with a median follow-up of 5 years). Inclusion criteria were: “type 2 diabetes mellitus at 30 years of age or older, an age of at least 55 years at the time of study entry, and a history of major macrovascular or microvascular disease or at least one other risk factor for vascular disease”\(^{(15)}\). Exclusion criteria were: “definite indication for, or contraindication to, any of the study treatments or a definite indication for long-term insulin therapy at the time of study entry”\(^{(15)}\).

A total of 12,877 patients were referred and 11,140 were recruited and randomized to treatment either with intensive glucose control (defined as the use of gliclazide plus other drugs as required to achieve a glycated hemoglobin value of 6.5% or less; \(n=5571\)) or standard glucose control (with target glycated hemoglobin levels defined on the basis of local guidelines; \(n=5569\)).

The primary study outcomes were a composite of macrovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and a composite of microvascular events (new or worsening nephropathy or retinopathy).

Some of the main results are shown in Table X. A reduction in the incidence of nephropathy was seen in patients under intensive glucose control.

<table>
<thead>
<tr>
<th></th>
<th>Intensive therapy ((n=5128))</th>
<th>Intensive therapy ((n=5123))</th>
<th>Hazard ratio (95% CI)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>352 (6.9)</td>
<td>371 (7.2)</td>
<td>0.90 (0.78-1.04)</td>
<td>0.16</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>257 (6.9)</td>
<td>203 (4.0)</td>
<td>1.22 (1.01-1.46)</td>
<td>0.04</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>135 (2.6)</td>
<td>94 (1.8)</td>
<td>1.35 (1.04-1.76)</td>
<td>0.02</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>186 (3.6)</td>
<td>235 (4.6)</td>
<td>0.76 (0.62-0.92)</td>
<td>0.004</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>67 (1.3)</td>
<td>61 (1.2)</td>
<td>1.06 (0.75-1.50)</td>
<td>0.74</td>
</tr>
<tr>
<td>Fatal or nonfatal congestive heart failure</td>
<td>152 (3.0)</td>
<td>124 (2.4)</td>
<td>1.18 (0.93-1.49)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hypoglycemic episodes requiring medical assistance</td>
<td>538 (10.5)</td>
<td>179 (3.5)</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean HbA1c at the end of the study (%) (baseline 8.1%)</td>
<td>6.4</td>
<td>7.5</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Primary outcome: first occurrence of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes; CI: confidence interval; HbA1c: glycated hemoglobin. Data adapted from\(^{(15)}\).
(4.1% vs. 5.2%; hazard ratio, 0.79; 95% CI, 0.66 to 0.93; \( p=0.006 \)). No significant findings were noted regarding total death rate, myocardial infarction, stroke or retinopathy. Severe hypoglycemic events were significantly more common in the intensive glucose control group. Mean systolic blood pressure was significantly lower at the end of the study in the intensive control group compared to the standard control group.

### 2.8. VADT (2009)

The VADT (Veterans Affairs Diabetes Trial) was a randomized controlled trial conducted at 20 VA medical centers. Its main findings were published in 2009\(^{16}\). The study was carried out from December 2000 to May 2008 (with a median follow-up of 5.6 years). Patients were included if there was “an inadequate response to maximal doses of an oral agent or insulin therapy”\(^{16}\). Exclusion criteria included “a glycated hemoglobin level of less than 7.5%, the occurrence of a cardiovascular event during the previous 6 months, advanced congestive heart failure, severe angina, a life expectancy of less than 7 years, a body-mass index (BMI) of more than 40, a serum creatinine level of more than 1.6 mg per deciliter and an alanine aminotransferase level of more than three times the upper limit of the normal range”\(^{16}\).

A total of 2239 patients were referred and 1791 were recruited and randomized to treatment either with intensive glucose control (metformin plus rosiglitazone if BMI \( \geq 27 \), glimepiride plus rosiglitazone if BMI <27, 892 patients started on maximal doses) or standard glucose control (the same drugs but on half the maximal doses, started on 899 patients). Insulin could be added at a later stage, if glycated hemoglobin was not under 6% (intensive arm) or 9% (standard arm). According to the study protocol, “the goal for glycated hemoglobin levels was an absolute reduction of 1.5 percentage points in the intensive-therapy group, as compared with the standard-therapy group”\(^{16}\). Details on the actual use of drugs were not given in the main publication\(^{16}\). Therapy for other cardiovascular risk factors was administered – aspirin and statins were routinely prescribed.

The primary study outcome was the time to first occurrence of any of a composite of cardiovascular events, including myocardial infarction, stroke, death from cardiovascular causes and new or worsening congestive heart failure\(^{16}\). Some of the main results are shown in Table XI. There were no significant differences in the outcomes reached by the two study groups of patients, not even in microvascular complications. Hypoglycemia and dyspnea were significantly more common in the intensive therapy group\(^{16}\). The authors concluded that “for now,
appropriate management of hypertension, dyslipidemia, and other cardiovascular risk factors appears to be the most effective approach to preventing cardiovascular morbidity and mortality.  

3. OTHER RELEVANT CLINICAL TRIALS

3.1 STENO-2 (2003, 2008)

The STENO-2 Study was a randomized, open, parallel trial, in which 160 patients with type 2 diabetes and persistent microalbuminuria were studied. The main results were published in 2003 and a follow-up paper was published in 2008. Conventional multifactorial treatment was compared to intensive therapy (80 patients in each arm). Intensive therapy had goals of “glycated hemoglobin less than 6.5%, total cholesterol less than 175 mg per deciliter, triglyceride level less than 150 mg per deciliter, systolic blood pressure less than 130 mm Hg and diastolic blood pressure less than 80 mm Hg”. The mean treatment period was 7.8 years, with an additional observational period of 5.5 years.

In both groups, the drugs used to achieve the treatment goals were metformin, gliclazide, insulin, atorvastatin (or another statin), fibrates, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, thiazides, calcium channel blockers, and beta-blockers. Aspirin was used in patients in the intensive therapy group, and so were several vitamins.

In the 2003 paper, the primary endpoint was a composite of death from cardiovascular causes, nonfatal myocardial infarction, coronary revascularization, nonfatal stroke, amputation as a result of ischemia, or vascular surgery for peripheral atherosclerotic artery disease. Patients in the intensive therapy group were more likely to be using an ACE inhibitor, an angiotensin II receptor antagonist, both of these types of drugs, a statin, aspirin and vitamin-mineral supplement. Some of the main results are shown in Table XII.

In the 2008 follow-up paper, the primary endpoint at 13.3 years of follow-up was the time to death from any cause. After the treatment period of 7.8 years was over, both groups of patients were informed about the benefits of intensified multifactorial treatment. Significantly more patients in the intensive therapy group used metformin or sulfonylurea. In the 5.5-year observational period, a total of 55 patients in the intensive therapy group and 38 patients in the conventional therapy group completed the follow-up study. Mean values for the intensive therapy group of 160±55 mg/dl for fasting plasma glucose and of 7.7±1.2% for glycated hemoglobin were seen, the corresponding values for the conventional therapy group being 170±61 mg/dl and 8.0±1.4%. Some of the main results are shown in Table XIII.

3.2 PROACTIVE (2005)

The PROACTIVE study (Prospective Pioglitazone Clinical Trial In Macrovascular Events) was a prospective, randomized, con-
trolled trial designed to ascertain whether pioglitazone reduces macrovascular morbidity and mortality in high-risk patients with type 2 diabetes. The study was carried out from May 2001 to January 2005, with a mean observation time of 34.5 months. Inclusion criteria were: patients with type 2 diabetes, aged 35–75 years, with a glycated hemoglobin concentration greater than 6.5%, despite previous treatment with diet alone or with oral glucose-lowering agents with or without insulin; presence of macrovascular disease prior to recruitment.

A total of 5238 patients were enrolled and randomized. A group of 2605 patients were assigned to oral pioglitazone, titrated from 15 mg to 45 mg, and 2633 patients were assigned to matching placebo, in addition to their previous glucose-lowering drugs and other medications. Therapy was prescribed in accordance with defined guidelines, which included a glycated hemoglobin target of <6.5%, optimum lipid-altering treatment, antiplatelet drugs, and antihypertensive therapy.

The primary endpoint was “the composite of all-cause mortality, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle”.<sup>19</sup> The main secondary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction, and stroke. A total of 514 of 2605 patients in the pioglitazone group and 572 of 2633 patients in the placebo group had at least one event in the primary composite endpoint (HR 0.90, 95% CI 0.80-1.02, p=0.095). A total of 301 patients in the pioglitazone group and 358 in the placebo group reached the main secondary endpoint (HR 0.84, 95% CI 0.72–0.98, p=0.027). Some of the main results are summarized in Table XIV.

Median values for HbA1c were 7.8% in the pioglitazone group and 7.9% for the placebo group. A larger decrease in HbA1c (0.8%) was seen with pioglitazone than with placebo (0.3%). A more favorable effect of pioglitazone (com-

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**Table XII.** Some major findings of the Steno-2 study (2003). Changes at the end of the study.

<table>
<thead>
<tr>
<th></th>
<th>Conventional therapy (n=63)</th>
<th>Intensive therapy (n=67)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm/Hg)</td>
<td>-3±3</td>
<td>-14±2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>-8±2</td>
<td>-12±2</td>
<td>&lt;0.006</td>
</tr>
<tr>
<td>Glycated hemoglobin (%)</td>
<td>-0.2±0.3</td>
<td>-0.5±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Composite cardiovascular endpoint *</td>
<td>85</td>
<td>-33</td>
<td>0.007</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>7</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>17</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>20</td>
<td>3</td>
<td>-</td>
</tr>
</tbody>
</table>

*: death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, amputation or surgery for peripheral atherosclerotic artery disease. Data adapted from <sup>17</sup>.

**Table XIII.** Some major findings of the Steno-2 study (2008 follow-up).

<table>
<thead>
<tr>
<th></th>
<th>Intensive therapy Number of patients/events</th>
<th>Conventional therapy Number of patients/events</th>
<th>Hazard ratio (95%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause</td>
<td>24</td>
<td>40</td>
<td>0.54 (0.32-0.89)</td>
<td>0.02</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>9</td>
<td>19</td>
<td>0.43 (0.19-0.94)</td>
<td>0.04</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>8/9</td>
<td>21/35</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stroke</td>
<td>6</td>
<td>13/60</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Numbers of deaths from any cause, deaths from cardiovascular causes, myocardial infarction and stroke at 13.3 years. CI: confidence interval. Data adapted from <sup>18</sup>.
pared to placebo) was also seen for plasma triglycerides, high density lipoprotein cholesterol and blood pressure. Mean bodyweight increased by 3.6 kg in the pioglitazone group, and decreased by 0.4 kg in the placebo group. Both insulin and metformin were used significantly more often in the placebo group than in the pioglitazone group. Heart failure was more common in the pioglitazone group; deaths from heart failure, however, were similar in both groups of patients. Fewer patients in the pioglitazone group were admitted to hospital.

3.3 ADOPT (2006)

The ADOPT study (A Diabetes Outcome Progression Trial) was a multicenter, randomized, double-blind, controlled clinical trial designed to evaluate the durability of glycemic control in patients receiving monotherapy with rosiglitazone, metformin, or glyburide (glibenclamide)\(^{(20)}\). It took place between April 2000 and June 2006. The median duration of treatment was 4.0 years for rosiglitazone and metformin and 3.3 years for glyburide. Patients were included with ages of 30 to 75 years, with fasting plasma glucose levels of 126 to 180 mg/dl. Patients with previous major cardiovascular disease were excluded, as well as those with significant hepatic disease, renal impairment or a history of lactic acidosis.

A total of 4360 patients were studied, 1456 under rosiglitazone therapy (4 mg initial, up to 4 mg twice daily), 1454 with metformin (500 mg initially, up to 1 g twice daily) and 1441 with glyburide (2.5 mg initial, up to 7.5 mg twice daily). The dosage of each drug was increased if fasting plasma glucose was ≥140 mg/dl.

According to the study protocol, “the primary outcome was the time from randomization to treatment failure, which was defined as confirmed hyperglycemia” (FPG >180 mg/dl)\(^{(20)}\). Monotherapy failure for glycemic control was seen in 2.9 per 100 patient-years under rosiglitazone therapy, the corresponding values for metformin being 4.3 and for glyburide 7.5. Weight gain was seen with rosiglitazone (4.8 kg) and glyburide (1.6 kg), whereas metformin therapy was associated with weight loss (2.9 kg). Rosiglitazone therapy was also associated with more frequent edema, higher levels of low-density lipoprotein cholesterol and a reduction in hematocrit. Metformin therapy, on the other hand, was associated with gastrointestinal side effects. Glyburide therapy was associated with more frequent hypoglycemia. Major cardiovascular results are summarized in Table XV. The authors stated “Glyburide was associated with a lower risk of cardiovascular events (including congestive heart failure) than was rosiglitazone (p<0.05), and the risk associated with metformin was similar to that with rosiglitazone”\(^{(20)}\).

3.4 RECORD (2007 interim report)

The RECORD study was a randomized, multicenter, open-label trial in which 4447 patients with type 2 diabetes who had inadequate glycemic control while receiving metformin or sulfonylurea were studied\(^{(21)}\). An interim analysis was published in 2007\(^{(21)}\) following the release of a meta-analysis\(^{(26)}\) suggesting an increased risk of myocardial infarction and death from cardiovascular causes associated

### Table XIV. Some major findings of the PROACTIVE study.

<table>
<thead>
<tr>
<th>First events (total events)</th>
<th>Pioglitazone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=2605)</td>
<td>(n=2633)</td>
</tr>
<tr>
<td>Death</td>
<td>177 (177)</td>
<td>186 (186)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>119 (131)</td>
<td>144 (157)</td>
</tr>
<tr>
<td>Stroke</td>
<td>86 (92)</td>
<td>107 (119)</td>
</tr>
<tr>
<td>Total events</td>
<td>203</td>
<td>900</td>
</tr>
</tbody>
</table>

HR: hazard. CI: confidence interval. A composite parameter including death, nonfatal myocardial infarction and stroke reached significance, in favor of pioglitazone (see text). Data adapted from\(^{(19)}\).
with rosiglitazone treatment of type 2 diabetes. The inclusion criteria were: patients with type 2 diabetes, aged 40 to 75 years old, with a body mass index of over 25.0, and a glycated hemoglobin (Hb Aic) level of more than 7.0% and less than or equal to 9.0% while receiving maximum doses of metformin or a sulfonylurea. Exclusion criteria were “the current use of other glucose-lowering agents, hospitalization for a major cardiovascular event in the previous 3 months, a planned cardiovascular intervention, heart failure, clinically significant hepatic disease, renal impairment, and uncontrolled hypertension”  

The rosiglitazone study group (rosiglitazone plus metformin or sulfonylurea – 2220 patients) was compared to the control group (metformin plus sulfonylurea – 2227 patients). Throughout the study, if (Hb Aic) exceeded 7.0%, dosages of the study drugs were increased. If (Hb Aic) exceeded 8.5% while patients were receiving the maximum tolerated dose, a third agent was added to the rosiglitazone group or insulin was initiated in the control group. If the (Hb Aic) level exceeded 8.5% in patients receiving triple therapy, rosiglitazone was stopped and insulin therapy started.  

According to the study protocol, “the primary endpoint was hospitalization (for acute myocardial infarction, congestive heart failure, stroke, unstable angina pectoris, transient ischemic attack, unplanned cardiovascular revascularization, amputation of extremities, or any other definite cardiovascular reason) or death from cardiovascular causes (including heart failure, acute myocardial infarction, sudden death, and death caused by acute vascular events including stroke)”  

Table XV. Some major findings of the ADOPT Study

<table>
<thead>
<tr>
<th></th>
<th>Rosiglitazone (n=1456) Serious/total events (%)</th>
<th>Metformin (n=1454) Serious/total events (%)</th>
<th>Glyburide (n=1441) Serious/total events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>49 (3.4)/62 (4.3)</td>
<td>46 (3.2)/58 (4.0)</td>
<td>26 (1.8)*/41 (2.3)</td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>2 (0.1)/2 (0.1)</td>
<td>2 (0.1)/2 (0.1)</td>
<td>3 (0.2)*/3 (0.2)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>22 (1.5)/25 (1.7)</td>
<td>18 (1.2)/21 (1.4)</td>
<td>11 (0.8)/15 (1.0)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(investigator reported)</td>
<td>12 (0.8)/22 (1.5)</td>
<td>12 (0.8)/19 (1.3)</td>
<td>3 (0.2)<em>/0.6)</em></td>
</tr>
<tr>
<td>Stroke</td>
<td>13 (0.9)/16 (1.1)</td>
<td>17 (1.2)/19 (1.3)</td>
<td>12 (0.8)/17 (1.2)</td>
</tr>
</tbody>
</table>

*: p<0.05 vs. rosiglitazone. Data adapted from (20).

with rosiglitazone treatment of type 2 diabetes. The inclusion criteria were: patients with type 2 diabetes, aged 40 to 75 years old, with a body mass index of over 25.0, and a glycated hemoglobin (Hb Aic) level of more than 7.0% and less than or equal to 9.0% while receiving maximum doses of metformin or a sulfonylurea. Exclusion criteria were “the current use of other glucose-lowering agents, hospitalization for a major cardiovascular event in the previous 3 months, a planned cardiovascular intervention, heart failure, clinically significant hepatic disease, renal impairment, and uncontrolled hypertension.”

The rosiglitazone study group (rosiglitazone plus metformin or sulfonylurea – 2220 patients) was compared to the control group (metformin plus sulfonylurea – 2227 patients). Throughout the study, if (Hb Aic) exceeded 7.0%, dosages of the study drugs were increased. If (Hb Aic) exceeded 8.5% while patients were receiving the maximum tolerated dose, a third agent was added to the rosiglitazone group or insulin was initiated in the control group. If the (Hb Aic) level exceeded 8.5% in patients receiving triple therapy, rosiglitazone was stopped and insulin therapy started.

According to the study protocol, “the primary endpoint was hospitalization (for acute myocardial infarction, congestive heart failure, stroke, unstable angina pectoris, transient ischemic attack, unplanned cardiovascular revascularization, amputation of extremities, or any other definite cardiovascular reason) or death from cardiovascular causes (including heart failure, acute myocardial infarction, sudden death, and death caused by acute vascular events including stroke)”

The outcome was analyzed as the time to first occurrence. The adjudicated primary end-point was reached in 217/2220 patients in the rosiglitazone group and in 202/2227 patients in the control group (hazard ratio 1.08, 95% CI 0.89-1.31, p=0.43). Some of the main results are shown in Table XVI. The authors concluded that “the data were insufficient to determine whether the drug was associated with an increase in the risk of myocardial infarction.”

### 3.5 CHICAGO (2006)

The CHICAGO (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone) trial was a randomized controlled trial, the main findings of which were published in 2006.

The study was carried out from October 2003 to May 2006 (with a treatment period of 72 weeks). Patients with type 2 diabetes, diet-controlled (with glycated hemoglobin between 6.5% and 10%) or treated with sulfonylurea, metformin, sulfonylurea plus metformin, or any of these plus insulin (with HbA1c between 6.5% and 10%) or treated with sulfonylurea, metformin, sulfonylurea plus metformin, or any of these plus insulin (with HbA1c between 6.5% and 9%), were included in the study. Exclusion criteria included major cardiovascular disease such as symptomatic coronary artery disease, cerebrovascular disease and advanced heart failure.

A total of 1346 patients were assessed for eligibility and 462 were randomized (aged 45-85 years, mean duration of diabetes of 7.7±2.2 years) for treatment either with pioglitazone, 15-45 mg/d (n=232) or glimepiride, 1-4 mg/d (n=230). Drug doses were titrated in order to maintain a fasting plasma glucose
level of 140 mg/dl or lower. Metformin or insulin was added in either group when the glycemic goal was not achieved.

The primary endpoint of this study was absolute change from baseline to final visit in mean posterior-wall carotid intima-media thickness in the right and left common carotid arteries. Absolute change in maximal carotid intima-media thickness was a secondary endpoint. Hypoglycemia occurred in 45/230 patients in the pioglitazone group and 53/228 in the glimepiride group, the corresponding figures for peripheral edema being 30 and 16 respectively. Significantly different effects were seen at the end of the study for glycated hemoglobin levels (pioglitazone-glimepiride difference at final visit -0.32%, 95% CI, -0.52% to -0.12%; p=0.002), high-density cholesterol levels (pioglitazone-glimepiride difference at final visit 6.4 mg/dl, 95% CI, 5.0 to 7.9 mg/dl, p<0.001) and triglyceride levels (decreased 13.5% with pioglitazone, increased 2.1% with glimepiride, treatment difference, 15.6%, 95% CI, 24.0% to 7.3%; p<0.001).

Progression of mean posterior wall carotid intima-media thickness was -0.001 mm for pioglitazone and +0.012 mm for glimepiride, corresponding to a difference of -0.013 mm, with 95% CI of -0.024 to -0.002 and p=0.02. For maximum posterior wall carotid intima-media thickness, the corresponding values were 0.002 mm for pioglitazone and 0.026 mm for glimepiride, a difference of -0.024 mm, with a 95% CI of -0.042% to -0.006% and p=0.008. The authors concluded that “over an 18-month treatment period in patients with type 2 DM, pioglitazone slowed progression of CIMT compared with glimepiride” (DM: diabetes mellitus; CIMT: carotid intima-media thickness).

### 3.6 PERISCOPE (2008)

The PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) Trial was a randomized controlled trial, the main findings of which were published in 2008. The study ran from August 2003 to March 2006 (treatment period of 18 months). Patients with type 2 diabetes, diet-controlled (with glycated hemoglobin between 6.5% and 10.0%) or receiving a glucose-lowering medication (glycated hemoglobin between 6.5% and 9%), were included in the study. Patients were required to undergo coronary angiography for clinical indications that demonstrated at least one angiographic stenosis with at least 20% narrowing.

A total of 1636 patients were referred and 547 were recruited (aged 35-85 years) and randomized to treatment either with pioglitazone (n=274) or glimepiride (n=273). Drug doses were titrated in order to maintain a fasting plasma glucose level of 140 mg/dl or lower. Glimepiride was used in doses of 1 to 4 mg/day and pioglitazone of 15 to 45 mg/day. Metformin, insulin, or both were added in either group when the glycemic goal could not be achieved.

The study protocol defined one primary intravascular ultrasonography (IVUS) endpoint – change in percent atheroma volume – and three secondary IVUS endpoints. A second intravascular study was performed in 181 glimepiride patients and in 179 patients in the
pioglitazone group.

Patients under pioglitazone treatment had a non-significant decrease of least square mean change in percent atheroma volume of 0.16% from baseline to final visit (95% CI, -0.57% to 0.25%). This value was significantly different from the change associated with glimepiride therapy, a mean increase of 0.73% (95% CI, 0.33% to 1.12%).

Glycated hemoglobin decreased in both study groups, but more so in the pioglitazone group (mean post-randomization value of 6.9% for pioglitazone and 7.0 for glimepiride). More favorable effects of pioglitazone were also seen with high density cholesterol, triglycerides and high-sensitivity C reactive protein. Pioglitazone, on the other hand, was associated with greater weight gain. Hypoglycemia was more common with glimepiride and peripheral edema more common with pioglitazone. Three percent of patients under pioglitazone had fractures, compared to none in the glimepiride group. The authors concluded that “treatment with pioglitazone resulted in a significantly lower rate of progression of coronary atherosclerosis compared with glimepiride” (23).

4. META-ANALYSES

Several meta-analyses of interest have been published (24-27). Space limitations preclude a detailed analysis in the present text.

5. OBSERVATIONAL (POPULATION-BASED) STUDIES

Several observational studies of interest have been published (28-46). Space limitations preclude a detailed analysis in the present text.

6. COMMENTS

Types 1 and 2 diabetes act as rather different entities in terms of etiopathogenesis, since a lack of insulin is found in one, whereas the opposite frequently occurs in the other. Type 2 diabetes, currently the most common type, appears to act as a risk factor for cardiovascular disease, and many diabetic patients die of cardiovascular disease (47). Glycated hemoglobin has been shown to act as an independent risk factor for coronary disease (48). A correlation has been described between plasma glucose and the angiographic importance of coronary disease (49).

Since insulin lowers plasma glucose, early demonstration of the dramatic effects of insulin use in type 1 diabetes has led both practitioners and researchers into thinking that lowering plasma glucose, by whatever means, would be of critical interest in the treatment of type 2 diabetics. Specifically, it has been hypothesized that restoring near-normal plasma glucose levels would reduce cardiovascular disease in these patients – thus decreasing parameters such as mortality rate, myocardial infarction and stroke.

The data reviewed in the present text fail to confirm this hypothesis. As early as 1970 and 1975, findings from the UGDP study showed a lack of relation between glucose lowering and cardiovascular mortality (7,8). This subject became the subject of considerable debate once again in 2008, when the ACCORD study was published, showing higher mortality in the intensive therapy group, patients with lower levels of glycated hemoglobin (14). Two other major studies published recently, ADVANCE (15) and VADT (16), failed to show a significant effect of hypoglycemic therapy on rates of major cardiovascular events or death. In Table XVII, a general overview of data from different clinical trials studying various types of hypoglycemic therapy, glycemic results, and cardiovascular results is presented. What seems to come out of the available data is that no consistent association between lowering plasma glucose and major cardiovascular disease and mortality rate has been demonstrated.

An exception to the general picture may be provided by the UKPDS 34 study (12), which showed that intensive treatment with metformin caused a reduction in mortality and myocardial infarction in overweight patients, compared to conventional treatment. The interest of metformin therapy is further supported by population studies such as the report by Simpson et al., indicating a relatively favorable effect of the drug (32). Metformin is a biguanide
drug (N,N-dimethyl biguanide), and is believed to decrease hepatic glucose production, increase peripheral glucose utilization, and decrease plasma levels not only of glucose, but also of insulin\(^{(56)}\). Metformin is closely related to phenformin in its chemical structure\(^{(31)}\). However, different cardiovascular outcomes may be found when results obtained with the two drugs are compared (taking UGDP into consideration, on the one hand, and UKPDS 34, on the other).

Also of interest are the results of the UKPDS 80 study, reporting on a 10-year post-trial follow-up\(^{(13)}\). A decrease in mortality and in the incidence of myocardial infarction were seen\(^{(13)}\). As hypothesized in type 1 diabetes, the beneficial effect of intensive therapy on the risk of cardiovascular disease could be the result of the reduction in the incidence of nephropathy\(^{(32)}\). The authors have termed this possible long-term phenomenon a “legacy effect”\(^{(13)}\). However, the results from UKPDS 80 were obtained in 79% of the patients who underwent randomization in the original UKPDS – therefore including patients that had already survived long enough to enter the post-trial follow-up. It is also noteworthy that patients with major cardiovascular disease were excluded from the original UKPDS study (see section 2.3 above).

Studying a significantly different population, with a large percentage of patients with previous cardiovascular disease and regularly using antiplatelet drugs and lipid-lowering therapy, the VADT trial showed an absence of effects of hypoglycemic therapy on mortality and cardiovascular disease\(^{(16)}\). The VADT study, however, studied mostly male patients.

Looking once again at the overall picture on mortality and cardiovascular disease presented in Table XVII, it is hard to find evidence in favor of lowering glycated hemoglobin levels to values under 7%. The only major trial indicating any benefit in proceeding in such a way is the ADVANCE trial, which showed an effect mainly on nephropathy (mainly albuminuria)\(^{(15)}\). Clearly, it is difficult to claim any value in lowering glycated hemoglobin levels to under 7% on the basis of the UKPDS data, since neither UKPDS 33 nor UKPDS 34 reached a mean value under 7% (Table XVII).

The UKPDS study has raised concerns on the combination of metformin and a sulfonylurea\(^{(12)}\). Observational data pointing in the same direction regarding this association have been published by several groups. However, some data obtained in large populations failed to report any increase in risk associated with this drug combination. Clearly, confounding by indication (“the tendency for patients with more severe disease both to be exposed to more aggressive therapy and to be more likely to experience an adverse outcome”\(^{(53)}\) could be present in some of these studies. It is therefore difficult to reach a clear conclusion on this issue at this stage.

Differences in outcomes could exist with different sulfonylurea agents\(^{(53)}\). In the ADVANCE study, the use of gliclazide in the intensive glucose control group of patients was definitely not associated with any significant increase in cardiovascular endpoints\(^{(55)}\). There could be differences between sulfonylurea agents in their affinity for different types of potassium channels\(^{(54)}\).

There are interesting data concerning pioglitazone, a thiazolidinedione drug, both in clinical trials and in population data. Pioglitazone is believed to act by binding to peroxisome proliferator-activated receptor gamma\(^{(55)}\), but has also been shown to bind to a mitochondrial protein, mitoNEET\(^{(56)}\). Thiazolidinediones could also interact with Klotho\(^{(57)}\). They are believed to increase insulin sensitivi-
ty in peripheral tissues \(^{(21)}\); pioglitazone has been shown to decrease fasting insulin levels\(^{(21)}\).

Both data from meta-analyses \(^{(24,27)}\) and observational data\(^{(40,41)}\) raise concerns on the effects of rosiglitazone. Once again, as in the case of metformin/phenformin, there may not be a class effect in this case, particularly regarding cardiovascular outcomes, even though the drugs have similar chemical structures. It should be noted that many drugs interact with more than one biological system, not to mention other types of interactions, such as pharmacokinetic ones.

Krumholz and Lee stress that “we should not be surprised that different strategies may have different effects on patients beyond their effect on risk-factor levels”\(^{(58)}\). Data reviewed in the present text firmly support this concept.
Goodarzi and Psaty argue that “increases in levels of insulin, not glucose, may be etiologic in cardiovascular disease risk”\(^6\). Indeed, high insulin concentrations have been shown to act as an independent predictor of ischemic heart disease in men\(^59\). Insulin could play a role in cell proliferation in atherosclerosis\(^60\). Clearly, some of the most interesting results reviewed here were obtained with drugs that decrease plasma insulin levels, and not with therapies that increase plasma insulin as a means to decrease glycemic levels.

Diabetes is frequently seen in association with other diseases, such as hypertension, obesity, dyslipidemia and sleep apnea. Data from bariatric surgery have shown that “diabetes was...
completely resolved in 76.8% of patients and resolved or improved in 86.0% after surgery and weight loss, according to the meta-analysis by Buchwald et al. (61). Similar findings were seen with hypertension, dyslipidemia and sleep apnea, leading to the suggestion that this could be a reversible syndrome associated with excessive weight – a barisystemic syndrome (62).

7. CONCLUSIONS

The data reviewed in the present text fail to confirm the hypothesis presented – that control of plasma glucose levels would reduce cardiovascular disease in type 2 diabetic patients. No consistent relation between lowering plasma glucose and either mortality rate or major cardiovascular disease has been shown to exist. There are interesting data concerning drugs that lower plasma insulin levels, particularly metformin, but also, to a certain degree, pioglitazone. Also of interest are data on a possible legacy effect in long-term follow-up of patients previously under intensive plasma glucose lowering. Consistent evidence in favor of lowering glycated hemoglobin levels to values under 7% also seems to be lacking at present.

For the time being, efforts should be centered on interventions with clear evidence of benefit, such as treatment of hypertension, dyslipidemia and excessive weight.

Note added in proof: The final report from the RECORD trial was published in June 2009 (Home PD et al. Lancet 2009; 373: 2125-2135). The authors concluded that rosiglitazone “…is confirmed to increase the risk of heart failure and of some fractures, mainly in women” and that “…rosiglitazone does not increase the risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering drugs”.

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