Clin. Cardiol. 24, 151–158 (2001)

Oral Antidiabetic Treatment in Patients with Coronary Disease: Time-Related Increased Mortality on Combined Glyburide/Metformin Therapy over a 7.7-Year Follow-Up

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Summary

Background: A sulfonylurea—usually glyburide—plus metformin constitute the most widely used oral antihyperglycemic combination in clinical practice. Both medications present undesirable cardiovascular effects. The issue whether the adverse effects of each of these pharmacologic agents may be additive and detrimental to the prognosis for coronary patients has not yet been specifically addressed.

Hypothesis: This study was designed to examine the survival in type 2 diabetics with proven coronary artery disease (CAD) receiving a combined glyburide/metformin antihyperglycemic treatment over a long-term follow-up period.

Methods: The study sample comprised 2,275 diabetic patients, aged 45–74 years, with proven CAD, who were screened but not included in the bezafibrate infarction prevention study. In addition, 9,047 nondiabetic patients with CAD represented a reference group. Diabetics were divided into four groups on the basis of their therapeutic regimen: diet alone (n = 990), glyburide (n = 953), metformin (n = 79), and a combination of the latter two (n = 253).

Results: The diabetic groups presented similar clinical characteristics upon recruitment. Crude mortality rate after a 7.7-year follow-up was lower in nondiabetics (14 vs. 31.6%, $p < 0.001$). Among diabetics, 720 patients died: 260 on diet (mortality 26.3%), 324 on glyburide (34%), 25 on metformin alone (31.6%), and 111 patients (43.9%) on combined treatment ($p < 0.000001$). Time-related mortality was almost equal for patients on metformin and on combined therapy over an intermediate follow-up period of 4 years (survival rates 0.80 and 0.79, respectively). The group on combined treatment presented the worst prognosis over the long-term follow-up, with a time-related survival rate of 0.59 after 7 years, versus 0.68 and 0.70 for glyburide and metformin, respectively. After adjustment to variables for prognosis, the use of the combined treatment was associated with an increased hazard ratio (HR) for all-cause mortality of 1.53 (95% confidence interval [CI] 1.20–1.96), whereas glyburide and metformin alone yielded HR 1.22 (95% CI 1.02–1.45) and HR 1.26 (95% CI 0.81–1.96), respectively.

Conclusions: We conclude that after a 7.7-year follow-up, monotherapy with either glyburide or metformin in diabetic patients with CAD yielded a similar outcome and was associated with a modest increase in mortality. However, time-related mortality was markedly increased when a combined glyburide/metformin treatment was used.

Key words: coronary artery disease, diabetes mellitus, glibenclamide, glyburide, metformin

Introduction

Cardiovascular mortality is increased up to fourfold in diabetic patients compared with their nondiabetic counterparts.[1] The efforts to lessen mortality in this population were usually focused on reducing hyperglycemia.[2] Thus, the preoccupation with the control of serum glucose levels has outweighed other relevant aspects in the management of these patients. Factors such as dyslipidemia[3] and, principally, hypertension[4,5] were recently highlighted.

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Received: January 11, 2000
Accepted with revision: May 12, 2000

Another important factor that should be considered in this population is represented by the undesirable cardiovascular side effects from well-known and widely used oral antidiabetic drugs. In patients with non-insulin-dependent diabetes mellitus (NIDDM), clinical studies have reported a higher frequency of major cardiovascular events in those treated with sulfonylureas in the early 1970s.[6] The awareness regarding this issue has increased during recent years following the detection of harmful influences of sulfonylureas on the ischemic myocardial cell.[7,8] On the other hand, cardiovascular complications presumably associated with the use of metformin had also been reported during both short-term[9,10] and long-term follow-up.[11]

When oral antidiabetic monotherapy does not achieve the desired glycemic level, a combined treatment is implemented. A sulfonylurea—usually glyburide (generally known as glibenclamide in European countries)—plus metformin constitute the most widely used antihyperglycemic combination in clinical practice.[12] However, the safety of this therapeutic regimen for long-term treatment is questionable.[13] Recent communications from the United Kingdom Prospective Diabetes Study (UKPDS) report that metformin appears to be advantageous as first-line treatment in obese diabetics. It is intriguing to find that when metformin was prescribed in an unselected population [including both patients with and without coronary artery disease (CAD)] already treated with sulfonylureas, there was a significant increase in all-cause mortality.[14]

Thus, the issue whether the adverse cardiovascular effects of each of these medications may be additive and detrimental to the prognosis of patients with CAD is of paramount importance and has not yet been specifically addressed. This study examines the survival in patients with NIDDM and CAD receiving a glyburide/metformin combination over a 7.7- year follow-up period.

Patients and Methods

Subjects

The initial population consisted of 12,402 patients screened for participation but not included in the bezafibrate infarction prevention study.[15] Of these, 1,080 were excluded from final analysis because of missing data. Thus, the study sample was reduced to 11,322 patients, aged between 45 and 74 years, with a previous myocardial infarction (0.5 to 5 years prior to begin of follow-up) and/or stable anginal syndrome (within 2 years preceding inclusion). This cohort included 2,275 diabetics; the additional 9,047 nondiabetic patients with CAD represented a reference group.

The major exclusion criteria were permanent pacemaker implantation, cerebrovascular disease, chronic hepatic or renal disease, peripheral vascular disease, malignant diseases, estrogen replacement therapy, and insulin treatment. The complete list appears in a previously published report.[15]

Patients with a history or physician diagnosis of NIDDM were divided into four groups on the basis of their therapeutic screening: (1) patients on diet alone, (2) patients receiving glyburide, (3) patients on metformin, and (4) patients receiving a combination of glyburide and metformin. Mortality data were assessed separately for each group.

Laboratory Methods

Cooled blood samples, collected in the 18 participating centers using standard equipment and procedures, were transferred to the study's central laboratory. All analyses were performed on a Boehringer Hitachi (Mannheim, Germany) 704 random access analyzer using Boehringer diagnostic kits. Detailed data on laboratory methods are given in a previous report.[16] Briefly, glucose values were determined by the glucose determination-parallel performance (PAP) method, employing a BM/Hitachi 717/911 analyzer. Evaluation of triglycerides was performed by determination of total values (glucose and phospholipids-PAP high performance method). Cholesterol was determined by the cholesterol-PAP method.

Determination of Additional Variables

Medical history, clinical findings, and drug intake data were recorded by the interviewing physician. The diagnosis of CAD was made in patients with documented myocardial infarction or typical anginal syndrome, in whom there was also a positive exercise test, evidence of myocardial ischemia revealed by radionuclear studies, or at least 60% stenosis of one major coronary artery. Criteria for the diagnosis of myocardial infarction, anginal syndrome, hypertension, and congestive heart failure have been previously reported.[15]

Mortality data were obtained by matching the patients' identification number with their life status in the Population Registry. Death certificates and diagnosis upon hospital discharge were coded using the system described in the International Classification of Diseases (ICD-9), codes 410 to 414.[17]

Statistical Analysis

Continuous variables were reported as mean value ± standard deviation; significance was determined using the chi-square and Student's *t*-tests and set at $p < 0.05$. Data were analyzed using the SAS software (SAS Institute, Inc., Cary, N.C., USA).[18] Age-adjusted mortality rates per 1,000 person years were computed using a special SAS macro.[19] Actuarial survival curves by treatment groups were produced using the LIFETEST procedure (SAS Institute, Inc.).[20] The log-rank test was used for comparing the curves. Multivariate analysis of mortality was performed using the stepwise Cox proportional hazard model (proportional hazards regression [PHREG] procedure) to account for differing lengths of follow-up and correlation with covariates; hazard ratio and 95% confidence limits were calculated. The significance levels for entering and removing an explanatory variable were set at 0.15 and 0.10, respectively.

Results

Baseline Data

The diabetic population (n = 2,275) included 990 patients on diet only, 953 receiving glyburide, 79 receiving metformin, and 253 patients receiving both glyburide and metformin.

The main clinical and laboratory characteristics of patients, according to antidiabetic treatment, are presented in Table I. No significant age differences among the groups was documented. The majority of the patients in all groups were men. Weight and body mass index were both higher in patients treated with metformin. About 75% had sustained a myocardial infarction in the past, and about two-thirds had a history of anginal syndrome. Hypertension was found in less than half of the patients. No significant differences in the prevalence of these diseases was found among all four groups. The low prevalence of peripheral vascular disease was similar in all groups. The number of patients with a history of cerebrovascular accident was relatively small, appearing with a relatively higher, albeit nonsignificant frequency in the diet group. Nearly a half of the patients had smoked in the past; less than 20% were active smokers at the beginning of follow-up.

Mean fasting glucose and triglycerides levels were both significantly higher in the combined metformin/glyburide group. No significant differences among the groups were found for total and low-density lipoprotein (LDL) cholesterol.

In the 9,047 nondiabetics, compared with the 2,275 patients with NIDDM, a relatively lower proportion presented with an old myocardial infarction (70%; p = 0.002), anginal syndrome (59%), hypertension (31%), or peripheral vascular disease (3%) (p < 0.001 for all). The nondiabetics presented with total cholesterol and LDL cholesterol values similar to those of the four diabetic groups. However, glucose and triglycerides were significantly lower (p = 0.0001 for all).

Data regarding treatment with cardiovascular drugs in the four diabetic groups are presented in Table II. Nitrates, calcium antagonists, and antiplatelet drugs represented frequent associations; more than a half of the patients on diet and on pharmacologic treatment (either monotherapy or combined therapy) received these drugs. There were no significant differences in the proportion of patients treated with the various cardiovascular drugs.

Mortality Data

Patients were followed from 6.2 up to 9.0 years (mean follow-up 7.7 ± 1.5 years).

During this period, crude all-cause mortality was lower in the nondiabetic group (14 vs. 31.6%; p < 0.001). In the NIDDM group, 720 patients died: 260 on diet (mortality 26.3%), 324 treated with glyburide (34%), 25 treated with metformin (31.6%), and 111 patients (43.9%) receiving combined metformin/glyburide treatment (p < 0.000001).

TABLE I Baseline characteristics of the diabetic population

	Diet n = 990	Glyburide n = 953	Metformin n = 79	Combined[a] n = 253	p Value
Age (years)[b]	60.3 ± 6.5	59.8 ± 6.6	59.5 ± 6.8	60.7 ± 6.4	NS
Weight (kg)[b]	76 ± 13	77 ± 13	81 ± 17	75 ± 13	0.006
BMI[b]	27 ± 4	27 ± 4	29 ± 5	27 ± 4	0.002
Men (%)	76	76	66	66	0.007
Past myocardial infarction (%)	73	75	73	71	NS
Angina (%)	64	65	65	66	NS
Hypertension (%)	42	44	44	45	NS
Peripheral vascular disease (%)	8	8	7	7	NS
NYHA class 2 (%)	33	35	41	37	NS
Cerebrovascular accident (%)	4	3	0	2	NS
COPD (%)	4	3	3	4	NS
Smoking (%)					
Current	10	10	17	10	NS
Past	48	50	39	44	NS
Glucose (mg/dl)[b]	158 ± 59	185 ± 63	192 ± 70	221 ± 73	0.00001
Total cholesterol (mg/dl)[b]	225 ± 43	227 ± 45	224 ± 48	227 ± 42	NS
LDL-cholesterol (mg/dl)[b]	153 ± 36	154 ± 39	149 ± 33	151 ± 36	NS
Triglycerides (mg/dl)[b]	175 ± 116	187 ± 107	180 ± 89	203 ± 117	0.007

[a] Patients receiving simultaneously metformin and glyburide.

[b] Values are expressed as mean ± standard deviation.

Abbreviations: BMI = body mass index (calculated as the weight in kilograms divided by the square of the height in meters), COPD = chronic obstructive pulmonary disease, LDL = low-density lipoprotein, NS = not significant, NYHA - New York Heart Association classification.

TABLE II Distribution of cardiovascular drugs among the diabetic patients (percentages)

	Diet n = 990 %	Glyburide n = 953 %	Metformin n = 79 %	Combined [a] n = 253 %	p Value
Beta blockers	34	33	40	33	NS
Nitrates	56	56		56	NS
Calcium antagonists	54	54	60	55	NS
Antiarrhythmics	7	4	5	6	NS
Antihypertensives [b]	16	19	13	18	NS
Diuretics	19	21	24	20	NS
Potassium	6	6	5	8	NS
Digitalis	7	6	4	10	NS
Antiplatelets	57	53	57	52	NS
Anticoagulants	2	1	3	2	NS
ACE inhibitors	13	16	17	10	NS

[a] Patients receiving glyburide and metformin simultaneously.
[b] Other than beta blockers, calcium antagonists, diuretics, and ACE inhibitors.
Abbreviations: ACE = angiotensin converting enzyme, NS = not significant.

The diet group presented the lowest age-adjusted rates for both all-cause and ischemic heart disease mortality, defined according to the International Classification of Diseases code[17] (Fig. 1). Patients on glyburide alone or metformin alone exhibited intermediate values, with higher CAD mortality in the metformin group; however, all-cause mortality was similar in both groups. The highest mortality rates were observed among patients receiving combined glyburide/metformin therapy. For these patients, age-adjusted all-cause and CAD mortality rates/1,000 person-years were 75.8 and 31.2, respectively.

Actuarial survival curves for all-cause mortality for nondiabetics and for patients on diet, glyburide, metformin, and combined glyburide/metformin treatment are presented in Figure 2. The lowest mortality for NIDDDM patients was observed in the diet group. The metformin group presented the highest mortality along the first half of the follow-up period. Time-related mortality was almost equal for patients on metformin and on combined therapy over an intermediate follow-up period of 4 years (survival rates 0.80 and 0.79, respectively). However, the group receiving combined treatment presented the worst prognosis over the long-term follow-up, with a time-related survival rate of 0.59 after 7 years. Patients on monotherapy with both glyburide or metformin presented similar outcomes at the end of the follow-up, exhibiting survival rates of 0.68 and 0.70, respectively.

To assess the association between mortality and the cardiovascular status of patients in the different treatment groups, age-adjusted all-cause mortality rate per 1,000 person-years was determined in patients with and without a history of myocardial infarction, anginal syndrome, hypertension, and by functional capacity classes according to New York Heart Association (NYHA) classification (Table III). The highest mortality rates were invariably found in patients on combined treatment, regardless of the presence or absence of a history of myocardial infarction, anginal syndrome, or hypertension, and for all functional classification classes.

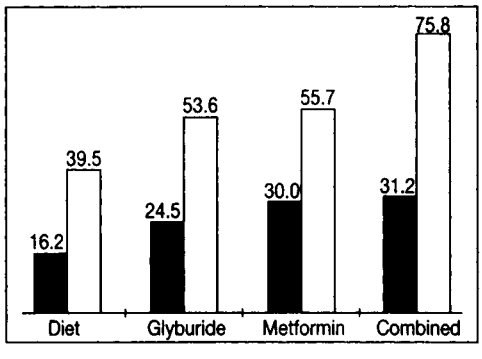

FIG. 1 Age-adjusted all-cause and ischemic heart disease (IHD) mortality rates/1000 person- years in non-insulin dependent diabetic patients according to treatment group. Patients on combined treatment received a combination of glyburide and metformin. ■ = IHD, □ = all-cause.

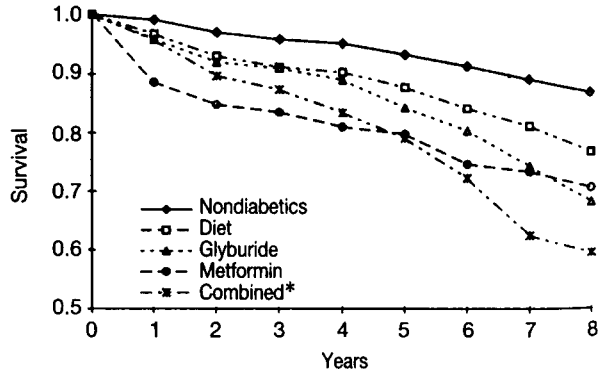

FIG. 2 Actuarial survival curves for all-cause mortality in nondiabetics and in non-insulin dependent diabetic patients on diet, glyburide, metformin, and combined glyburide/metformin treatment (*) after a follow-up period of 7.7 ± 1.5 years.

TABLE III Age-adjusted all-cause mortality rates/1,000 person-years among diabetic patients in the different treatment groups, according to presence or absence of prior myocardial infarction, anginal syndrome, hypertension, or the severity of functional class

	Diet	Glyburide	Metformin	Combined [a]
Myocardial infarction				
Present	43.5	58.4	74.4	79.5
Absent	29.9	40	18.1	63.2
Anginal syndrome				
Present	43.6	53.9	57.2	86.4
Absent	33	53	53.5	59.3
Functional class [b]				
Class 1	33.3	46.4	60.2	62.4
Class 2	53.8	71	54.1	107.6
Hypertension				
Present	51.5	59.1	22.9	83.9
Absent	31.2	49.7	85.1	69.6

[a] Patients receiving glyburide and metformin simultaneously.
[b] According to New York Heart Association classification.

A multivariate analysis was performed, taking into account age, gender, glucose, total cholesterol, triglycerides, previous myocardial infarction, functional class, hypertension, peripheral vascular disease, previous cerebrovascular accident, anginal syndrome, smoking, body mass index, and use of beta blockers and of antiplatelet drugs. After adjustment for these variables, with patients on diet as the reference group, the use of combined glyburide/metformin treatment was associated with a significantly higher hazard ratio (HR) of all-cause mortality—1.53 (95% CI 1.20–1.96)—compared with the other antihyperglycemic regimens. Further adjustment, performed for significant variables only (gender, weight, body mass index, glucose, and triglycerides) did not change the results (Table IV).

Discussion

A main goal of oral antihyperglycemic treatment in patients with NIDDM is to lower glucose levels to reduce the likelihood of macrovascular events that represent the major cause of mortality and morbidity in this type of diabetes.[1, 21] This purpose was not yet achieved, since blood-glucose control decreases the risk of microvascular but not macrovascular complications.[22] Thus, the potential adverse effects on the heart of antidiabetic drugs represent an important issue since, paradoxically, these medications might outbalance the benefits of glucose control and jeopardize cardiovascular prognosis. This point acquires special relevance when two antidiabetic preparations are simultaneously used in patients with established CAD during a prolonged time. Long-term prognosis of patients receiving a glyburide/metformin combination was first addressed by UKPDS. The UKPDS findings on increased all-cause mortality, while adding metformin to sulfonylureas in a population comprising patients both with and without CAD,[14] are disquieting.

To the best of our knowledge, the present report is the first one dealing with long-term survival in a large cohort of patients with NIDDM with proven CAD on several antidiabetic regimens. The principal observation derived from the results of this study is the substantially increased time-related mortality rate among patients receiving combined glyburide/metformin treatment. Augmented mortality rates were found in this group for all NYHA classification classes, disregarding the presence or absence of prior myocardial infarction, anginal syndrome, or hypertension.

TABLE IV Comparison of all-cause mortality in 1,285 diabetic patients on the basis of their antihyperglycemic therapeutic regimen with that of 990 diabetics on diet only during a 7.7-year follow-up

Therapeutic regimen	No. of patients	HR	95% CI	HR [b]	95% CI [b]
Glyburide	953	1.22	1.02–1.45	1.21	1.02–1.44
Metformin	79	1.26	0.81–1.96	1.19	0.76–1.84
Combined [a]	253	1.53	1.20–1.96	1.53	1.20–1.95

[a] Patients receiving glyburide and metformin simultaneously.
[b] Adjustment performed for significant variables only (gender, weight, body mass index, glucose, triglycerides).
Abbreviations: HR = hazard ratio; CI = confidence interval.

Glyburide and Myocardial Function

Glyburide is a sulfanylurea representing today a mainstay of therapy in patients with NIDDM. At cellular level, sulfonylureas exert their action by closing the adenosine triphosphate (ATP)-dependent potassium channels; this feature is responsible for both the insulinotropic effect and the adverse effects on the heart.[7, 8] In fact, these drugs have been reported to reduce resting myocardial blood flow,[23] to impair the recovery of contractile function after experimental ischemia,[24] to increase the ultimate infarct size,[25] to elicit proarrhythmic effects,[26] to abolish ischemic preconditioning in animal models,[27] and to increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction.[28] Prevention of myocardial preconditioning by glyburide was also demonstrated in clinical trials.[29] However, not all of the undesir-

able effects on cardiovascular outcome reported for the first-generation sulfonylureas such as tolbutamide[6] can be automatically extrapolated to more modern compounds such as glyburide, which is short acting and possesses antiarrhythmic properties.[7] In our population, age-adjusted mortality rates/1,000 person-years in the glyburide group in presence of myocardial infarction or angina were lower than the rates in patients treated with other pharmacologic regimens. Multivariate analysis demonstrated that, compared with patients on diet, time-related all-cause mortality was similar during the first half of the follow-up period, but increased for the glyburide group at the end of follow-up.

Metformin Therapy in Cardiac Patients

Metformin is the only drug belonging to the biguanide class currently available in most parts of the world. It reduces blood glucose levels through suppression of gluconeogenesis, stimulation of peripheral glucose uptake by tissue in the presence of insulin, and decreased absorption of glucose from the gastrointestinal tract. Unlike sulfonylureas, it does not produce hypoglycemia, may reduce body weight, and improves both blood lipid profile and fibrinolytic activity.[30]

However, metformin has some disadvantages that may influence the cardiovascular system. Gastrointestinal disturbances, such as diarrhea, are frequent, and the intestinal absorption of group B vitamins and folate is impaired during chronic therapy.[31] This deficiency leads to increased plasma homocysteine levels which, in turn, accelerate the progression of vascular disease due to adverse effects on platelets, clotting factors, and endothelium.[32] The existence of a graded association between homocysteine levels and overall mortality in patients with CAD is well established.[33]

In addition, metformin may lead to lethal lactic acidosis, especially in patients with clinical conditions that predispose to this complication, such as heart failure or recent myocardial infarction.[10] Thus, the use of this drug was discouraged in patients with NIDDM with known cardiac disease.[11,34] It should be remembered that another drug of the biguanide group, phenformin, was withdrawn in many countries during the 1970s because of its link to lactic acidosis. A possible association of phenformin with increased cardiovascular mortality has also been suggested.[35]

In our population, age adjusted all-cause and, more notably, CAD mortality rates/1,000 person-years were higher in the metformin group as a whole. In addition, patients with both anginal and postmyocardial infarction in this group presented with higher mortality than those treated with glyburide, but in absence of a prior infarction the patients on metformin demonstrated the lowest mortality compared with all other groups. At multivariate analysis, the time-related mortality was the highest across the first half of the follow-up period, but during the last year it was nearly equal to those of patients receiving glyburide.

Combined Antihyperglycemic Treatment

Combined therapy is based on the premise that pharmacologic agents acting via different mechanisms and presenting differing side effects permit the design of individualized antidiabetic regimens. This approach reflects the plausibility that monotherapy with any currently available oral medication is likely to fail over time in part of the patients. The present study represents the first report on long-term mortality data in patients with CAD receiving the commonly prescribed combined treatment with glyburide and metformin. Evidence regarding this type of treatment comes from studies with follow-up duration ranging from several weeks to 6 months only[12] or without a separate analysis of diabetic patients with CAD.[36]

Our combined group as a whole presented the highest age adjusted all-cause mortality rates/1,000 person-years compared with the other groups. This feature was also particularly evident in NYHA class 2 patients, in whom mortality was one-third higher than in patients treated with glyburide, and about 100% higher than in patients on diet or receiving metformin. At multivariate analysis, time-related mortality was also the highest through the second half of the follow-up period.

Patients in the four treatment groups exhibited a comparable cardiovascular status while entering into the study. The exaggerated mortality is seen only at long-term follow-up and its underlying mechanism is not fully understood. A possible explanation is that macrovascular derangement in diabetics takes several years to develop.[37] Then, the cumulative undesirable cardiovascular effects of both drugs affect an already weakened heart and the impact of medications on mortality will be time dependent, becoming evident only after a certain period of treatment.

Since baseline clinical characteristics of patients were similar, it seems conceivable that the particular therapeutic regimen in this group played a role in the strikingly different outcome. This is in keeping with our finding that in the subset of NYHA class 2 patients, those treated with combined therapy presented, by far, the worst prognosis.

Pharmacologic interaction between cardiovascular and antidiabetic drugs is an additional aspect that should be considered, since both glyburide and metformin effects can be potentiated by some widely used cardiovascular drugs. Metformin undergoes renal excretion. Thus, the coadministration of nifedipine, furosemide, digoxin, quinidine, and triamtirene—which are mainly eliminated by renal tubular secretion—may interact with metformin by competing for proximal renal tubular transport systems,[38] leading to increased metformin plasma levels. Similarly, angiotensin-converting enzyme inhibitors may increase the plasma concentration of sulfonylureas.[39]

Study Limitations

This is a retrospective observational study in which data have been prospectively collected for different purposes, and for which information regarding duration of diabetes and drug doses was not available. Therefore, caution should be used in interpreting our findings since it may be difficult, even in multivariate analysis, to distinguish between undesirable drug effects and those related to the degree of metabolic anomalies; glucose and triglycerides values at entry were higher in the group receiving combined therapy. In addition, no informa-

tion was available regarding hemoglobin A1c levels and protein excretion.

Despite these limitations, the results of this study have important implications in understanding the role of oral antidiabetic preparations on the outcome of CAD in patients with NIDDM. The large cohort of patients with both CAD and diabetes receiving various types of antidiabetic therapy allowed us to examine mortality rates separately in each treatment group. The pharmacologic management of diabetes in patients with CAD represents a difficult challenge; the findings of this long-term follow-up could guide the clinician toward a therapeutic approach aimed to optimize the outcome.

Clinical Implications

A sulfonylurea such as glyburide is conventionally the first choice of treatment in nonobese patients with NIDDM in whom dietary therapy fails to control glycemia adequately, but is not always effective (primary failure). Secondary failure occurs in patients who have taken a sulfonylurea to good effect initially, but subsequently become poorly controlled. When metformin is used as initial monotherapy—principally in obese patients—it yields clinical benefit, and primary and secondary failure rates are similar to those encountered with sulfonylurea treatment.[40] Our data demonstrate that long-term monotherapy with either of these medications in diabetics with CAD results in a similar outcome and is associated only with a modest increase in mortality. However, the adverse cardiovascular effects of each of these medications seem to be additive, and time-related mortality is markedly increased when a combination is used. These findings are in keeping with recent UKPDS findings showing that when metformin was prescribed in an unselected population already treated with sulfonylureas there was a significant increase in all-cause mortality.[14]

While the rate of cardiovascular disease has decreased in the general population, it has remained stable or even increased among diabetics;[41] data regarding long-term mortality in patients using several types of oral antidiabetic therapies are sparse. The major implication to be drawn from the present study is that combined glyburide/metformin therapy should be avoided in the long-term management of patients with NIDDM with proven CAD; alternative antidiabetic therapeutic approaches should be implemented in this population.

Appendix

Bezafibrate Infarction Prevention (BIP) Study Group

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