Is There Evidence That Oral Hypoglycemic Agents Reduce Cardiovascular Morbidity/ Mortality? Yes

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Although type 2 diabetes is a heterogeneous condition encompassing multiple metabolic and vascular alterations, it can be easily described as a disease characterized by chronic hyperglycemia and increased cardiovascular (CV) risk. Hyperglycemia is the diagnostic criterion for diabetes, the target for antidiabetic therapy, and, together with A1C, the marker of glycemic control. Progressive worsening of glycemic control has been described in type 2 diabetic patients irrespective of initial form of treatment, leading the U.K. Prospective Diabetes Study (UKPDS) investigators to describe such changes as the "natural history" of the disease (1). Still, maintaining good glycemic control is crucial, since it is associated with marked reduction in the risk of developing retinopathy, nephropathy, and neuropathy in both type 1 (2) and type 2 diabetic patients (1). But it is CV disease that worsens long-term prognosis in type 2 diabetes (3), to the point that diabetes has been proposed as a CV risk equivalent owed to the observation that 10-year risk for major coronary events approximates the risk in CHD in patients without diabetes with previous CV events (4), increased case fatality rate after myocardial infarction, and worse overall prognosis after CHD (5). In diabetic patients, even after correction for known CV risk factors, the incidence of myocardial infarction or stroke is two- to threefold higher than in the nondiabetic population, with a twofold increase in risk of death (6), suggesting that some fea-ture of diabetes must confer excessive propensity toward CV disease.

Can this feature be hyperglycemia? No better issue can be chosen for debate. From an epidemiological point of view, there is evidence that the risk of CV mortality increases with the increase of plasma glucose concentrations (7) and A1C values (8). Moreover, multiple atherogenic mechanisms have been identified that can be activated by hyperglycemia (9). In spite of evident plausibility for hyperglycemia as a CV risk factor itself, intervention data remain controversial. Even worse, results of recent large-scale intervention trials such as ACCORD (10), ADVANCE (11), and VADT (12) seem to undermine the concept that strict glycemic control may confer some protection against CV disease in people with type 2 diabetes. This apparent paradox can only be resolved by acknowledging the multifactorial nature of CV risk in diabetic patients (13). Many of these factors have emerged in the UKPDS as well (14). In a ranking analysis, A1C turned out to be the third most important factor in determining CV risk in type 2 diabetic patients (14). Therefore, antidiabetic drugs that reduce blood glucose levels while exerting some effect on CV risk factor should be expected to provide beneficial effects. Still, the potential role that available oral hypoglycemic agents may have on CV risk is an even more controversial issue. The debate on the safety issue of glitazones has not yet abated (15), so that assessing whether oral hypoglycemic agents may contribute to reduce CV morbidity/ mortality in type 2 diabetic patients becomes quite controversial and requires careful consideration of several important issues. First of all, the ratio between the blood glucose–lowering efficacy of oral hypoglycemic agents and their effects on vasculature and the heart has to be defined.

INSULIN
SECRETAGOGUES — Sulfonylureas have the longest record of use in diabetes management and have evolved in the past 50 years from first-, second-, and third-generation agents. Sulfonylureas enhance insulin secretion upon binding with β-cell membrane receptors to close SUR1/Kir6.2 channels. Blood glucose lowering accounts for 0.5–2% A1C reduction but, because of ensuing hyperinsulinemia, weight gain and hypoglycemia remain the main undesirable adverse effects. Last-generation sulfonylureas have been claimed to exert some effect on lipid profile, C-reactive protein, tumor necrosis factor-α, and plasma activator inhibitor (PAI)-1 concentrations, but these observations remain limited to small size study with uncertain clinical implications. Available outcome studies are largely based on first- and second-generation sulfonylureas and have led to conflicting results. The University Group Diabetes Project study (16) suggested increased CV risk in patients treated with tolbutamide, a first-generation sulfonylurea. These results have been widely criticized on the basis of study design flaws. Moreover, some evidence suggests greater risk of mortality with first-generation sulfonylureas compared with more recent ones.

Much debate was ignited by a marginally significant 16% ($P = 0.052$) reduction in fatal and nonfatal myocardial infarction in the UKPDS where chlorpropamide, glibenclamide, or glipizide were used as initial therapy in newly diagnosed uncomplicated diabetic patients (1). Of interest, however, this effect was achieved in the face of 4–5 kg body weight gain during follow-up. Whether the finding has to be seen as a positive one or not may

remain unsolved, but it rules out a detrimental effect of sulfonylureas on CV risk, something that was much feared on the basis of nonselective effects of these agents on pancreatic and cardiac K-ATPase channels. Interaction with cardiac SUR2A/Kir6 channels can impair ischemic preconditioning, exposing patients to increased CHD risk. On the other hand, experimental results show that inhibition of sarcolemmal K-ATPase channels reduces the incidence of lethal ventricular arrhythmias and improves survival both during acute myocardial infarction and reperfusion (17). Moreover, impairment of cardiac ischemic preconditioning does not seem to occur with more selective sulfonylureas such as glimepiride and gliclazide. The latter has been claimed to have some antioxidant and antiplatelet aggregatory effect, and it represents the base of the antidiabetic treatment in the ADVANCE trial (11). The study showed that intensive glycemic control initiated with gliclazide but maintained by adding multiple hypoglycemic agents as needed resulted in a nonsignificant 6% reduction of major macrovascular events (hazard ratio [HR] 0.94, 95% CI 0.84–1.06; $P = 0.32$). Altogether, it is possible to conclude that while no certain cardioprotective effect can be attributed to sulfonylureas, they do not seem to be a matter of concern, particularly if the latest compounds are chosen. This view is supported by large retrospective analysis that did not manage to identify a clear safety signal. For instance, analysis of databases of Diabetes Audit and Research in Tayside Scotland (DARTS) and Medicine and Monitoring Unit (MEMO) (18) suggested higher CV morbidity and mortality in the sulfonylurea-treated patients compared with those on metformin. On the contrary, Gulliford and Latinovic (19) failed to show a significant hazard ratio for all-cause mortality in diabetic subjects treated with sulfonylureas compared with those treated with metformin (HR 1.06, 95% CI 0.85–1.31; $P = 0.616$).

Meglitinides can be considered an evolution of sulfonylureas, since they are derived from nonsulfonylureic moiety of sulfonylureas. Similar to the latter, repaglinide and nateglinide enhance insulin secretion by binding the β-cell sulfonylurea receptor but at the level of a different subunit, resulting in a more rapid onset of action, shorter half-life, and more physiologic meal-related insulin response with reduced risk of severe hypoglycemia. Meglitinide treatment is associated with 0.5–0.8% A1C reduction. Small-size studies have indicated a limited effect on lipid profile, PAI-1, lipoprotein(a), homocysteine, C-reactive protein, and interleukin-6 concentration, similar, if not slightly better, to those observed with sulfonylureas (20). Some emphasis has been put on greater efficacy of meglitinides compared with sulfonylureas in controlling postprandial hyperglycemia, a parameter that has been associated with increased CV risk. Twelve-month treatment of diabetic patients with repaglinide or glyburide was associated with similar reduction of A1C (−0.9%) but lower postprandial glucose with the former (148 vs. 180 mg/dl). Treatment with repaglinide was also associated with a greater proportion of patients with regression (>0.020 mm) of carotid intima-media thickness (52 vs. 18%, $P < 0.01$) (20). Still, no data are yet available regarding meglitinide effects on major CV events. The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) is a multinational randomized double-blind placebo-controlled forced titration, 2×2 factorial design study designed to assess whether treatment with either agent can prevent development of type 2 diabetes and/or reduce the risk of CV disease (21). The results of the trials are not expected until the end of year 2009.

Metformin
Insulin resistance is a central pathogenetic mechanism of type 2 diabetes, which not only contributes to development of hyperglycemia but also confers an independent risk for CV disease. Moreover, insulin resistance plays an important role in the development of many of the disturbances encompassing the metabolic syndrome (22). Therefore, insulin sensitization is an attractive form of treatment in the attempt to improve metabolic control and reduce CV risk.

Metformin has been the only sensitizer available for many years. It exerts a prevalent effect on hepatic insulin sensitivity, although some action is played on skeletal muscle and adipose tissue as well. Metformin can reduce A1C by 0.5–1.5% and exerts beneficial albeit modest effects on traditional CV risk factors reducing blood pressure (23), improving lipid profile, and maintaining, if not lowering, body weight due to a mild anorexiant effect. Many studies, although not all of them, have shown that metformin can reduce oxidative stress and lipid peroxidation, improve the pro-fibrinolytic state by reducing the circulating levels of PAI-1 and von Willebrand factor, hamper platelet aggregation, lower low-grade inflammation, and improve endothelial function. It is on the basis of these pleiotropic effects that the positive outcomes of the UKPDS have been accounted for. Secondary analysis of 342 overweight diabetic patients treated with metformin (Fig. 1) showed greater beneficial effect on all diabetes-related end points, including a 39% risk reduction for myocardial infarction ($P = 0.01$) compared with 951 patients treated with sulfonylureas or insulin (24). Based on these results and retrospective analysis (19), a cardioprotective effect of metformin has been claimed (25) and metformin therapy has become a standard first-line treatment in almost all national and international guidelines.

Thiazolidinediones
Thiazolidinediones (TZDs) are agonists of the peroxisome proliferator–activated receptor (PPAR)-γ, which enhances insulin action primarily on the adipose tissue with a favorable effect exerted on skeletal muscle and liver as well (26). A bulk of preclinical as well as small-size clinical studies have focused on CV markers or intermediate atherosclerosis outcomes to provide the basis for postulating potential beneficial effects of these drugs on the CV risk of diabetic patients. Such a background has been extensively discussed in a recent review by McGuire and Inzucchi (27).

The typical A1C reduction associated with the use of rosiglitazone and pioglitazone ranges between 1.0 and 2.0%, but drug-specific changes in lipid profile is exerted by the two drugs. In head-to-head comparison and meta-analysis of the available studies (28), it was shown that pioglitazone lowers triglycerides and increases HDL cholesterol, with a neutral effect on LDL cholesterol, while rosiglitazone treatment is associated with an increase in HDL as well as total and LDL cholesterol, with a neutral effect on triglycerides. Besides these metabolic effects, TZDs can lower blood pressure, reduce microalbuminuria (29), and exert anti-inflammatory and anti-oxidative action along with an increase in adiponectin levels.

As mentioned, positive effects have been observed with respect to intermediate CV end points. For instance, TZD treatment is associated with improved endothelial function, larger number of dia-
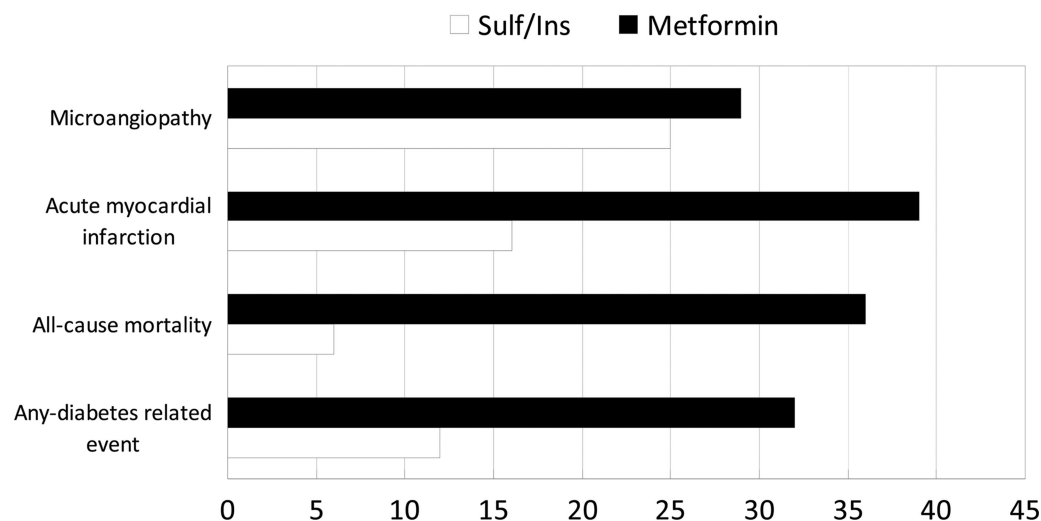
☐ Sulf/Ins   ■ Metformin

Figure 1—*Effect of sulfonylurea (Sulf) and metformin versus conventional blood glucose control on micro- and macrovascular diabetes complications in the UKPDS. Adapted from Ref. 1 for sulfonylureas or insulin (Ins) data and from Ref. 24 for metformin data.*

betic patients with regression of carotid intima-media thickness, and less re-stenosis after coronary artery stent implantation. More recently, the PERISCOPE study compared the effect of pioglitazone and glimepiride on progression of atherosclerosis by intravascular ultrasonography in type 2 diabetic patients and coronary artery disease (30). The trial showed a significantly lower rate of progression of coronary atherosclerosis with pioglitazone than with glimepiride therapy.

Of a number of large-scale randomized controlled clinical trials, only the results from the PROspective pioglitAzone Clinical Trial In macro-Vascular Events (PROACTIVE) trial (31) and an interim analysis of Rosiglitazone Evaluated for Cardiac Outcome and Regulation of glycemia in Diabetes (RECORD) (32) trial have been so far published. The PROACTIVE trial was a double-blind placebo-controlled study performed in 5,238 diabetic patients with established macrovascular complications randomized to either 45 mg/day pioglitazone or placebo added to existing antidiabetic treatment. Compared with placebo, pioglitazone treatment was associated with lower A1C (-0.6%), triglycerides (-21 mg/dl), systolic blood pressure (-3 mmHg), and higher HDL cholesterol (3.9 mg/dl). A significant reduction in the predefined secondary composite end point of all-cause mortality, nonfatal myocardial infarction, and stroke (HR 0.84, 95% CI 0.72–0.98; $P = 0.027$) was found, although primary composite end point (all-cause mortality, nonfatal myocardial infarction, stroke, major leg amputation,

acute coronary syndrome, cardiac or leg revascularization) did not reach statistical significance (31). A post hoc analysis in patients with previous myocardial infarction also showed the significant beneficial effect of pioglitazone on the prespecified end point of fatal and nonfatal myocardial infarction (20% risk reduction; $P = 0.045$) and acute coronary syndrome (37% risk reduction; $P = 0.035$). The potential reduction in atherosclerotic risk associated with pioglitazone is supported by the meta-analysis of 19 controlled studies showing lower risk for a composite of death/myocardial infarction/stroke (HR 0.82, 95% CI 0.72–0.94; $P = 0.005$) (33).

No completed long-term trials in diabetic patients are currently available for rosiglitazone. The RECORD trial has so far recorded no statistically significant difference in risk of hospitalization (HR 1.08, 95% CI 0.89–1.13; $P = 0.43$) or mortality (HR 0.83, 95% CI 0.67–1.27; $P = 0.46$) due to CV cause (32). The results have been essentially confirmed by the final study report (34). The interim analysis prompted by the publication of Nissen meta-analysis (35) reporting a significant increase in the risk of myocardial infarction (odds ratio 1.43, 95% CI 1.03–1.98; $P = 0.03$) and a nonsignificant increase in the risk of CV mortality (odds ratio 1.64, 95% CI 0.98–2.74; $P = 0.06$). That report generated much discussion due to limitations in the statistical analysis (27) and triggered further reassessment of available data leading to the uncertain effect of rosiglitazone on the risk of myocar-

dial infarction and death from CV causes (36).

Irrespective of the safety signal on myocardial infarction risk, both TZDs have been shown to cause weight gain, fluid retention, and edema and potentially worsen incipient congestive heart failure (CHF). In the PROACTIVE study, hospitalization for CHF occurred in 5.7% of patients treated with pioglitazone versus 4.1% treated with placebo ($P = 0.007$), with no evident increase in heart failure–associated mortality (25 [0.96%] vs. 22 [0.84%] cases) (31). In the RECORD study, incidence of hospitalization for CHF was higher in rosiglitazone-treated patients than in the control group (1.7 vs. 0.8%; $P = 0.006$) (32).

With such a contradictory scenario, how can we then reconcile positive and negative signals for efficacy and safety of TZDs on CV risk? There is no obvious answer to that, but several controlled trials in patients with different CV risk are still ongoing. While these studies should be carefully monitored, their results are much needed to gain a better assessment of the real impact of TZDs on the CV risk of type 2 diabetes. Still, a lesson is already available. Careful selection of patients indeed not only may reduce the risk of severe adverse events (in particular, CHF) (37), but it may also identify those individuals in whom greater metabolic and CV benefit may be ensured.

α-Glucosidase inhibitors
The α-glucosidase inhibitors act by blocking the action of intestinal α-glucosidase, which hydrolyzes diet-derived oli-

gosaccharides and polysaccharides. As a consequence, they slow carbohydrate digestion and absorption and reduce postprandial glucose excursion. This glucose-lowering effect results in 0.5–0.8% A1C reduction. A recent meta-analysis by Hanefeld et al. (38) confirms that along with improved glycemic control, acarbose also can lower triglyceride levels, body weight, and systolic blood pressure. When used in people with impaired glucose tolerance, acarbose slowed progression of carotid intima-media thickness with a 50% reduction in its annual increase compared with placebo. Moreover, in the STOP-NIDDM trial, a large multicenter double-blind placebo-controlled study performed to assess prevention of diabetes by acarbose in subjects with impaired glucose tolerance, a significant reduction in risk of myocardial infarction (HR 0.09, 95% CI 0.01–0.72; $P = 0.02$) and a 34% relative risk reduction in the incidence of new cases of hypertension (HR 0.66, 95% CI 0.49–0.89; $P = 0.006$) was observed (39). Although these results do require further confirmation (40), mechanisms that may account for this positive effect have been investigated (41). A major effect is attributed to prevention of a rapid raise in postprandial hyperglycemia, resulting in reduced oxidative stress and inflammatory response, fibrinogen concentration, macrophage adhesion to endothelium, and endothelial function. From this point of view, of interest are the similarities of the results obtained with metiglinides, i.e., another therapeutic approach associated with more effective postprandial glycemic control. Both treatments have been shown to improve regression of carotid intima-media thickness (20).

NEW DRUGS — New hypoglycemic agents have been recently introduced for treatment of type 2 diabetes. For these new agents, careful assessment of CV effects is still required, but they are worth mentioning because of some intriguing features. From a better understanding of the physiologic meaning of the entero-pancreatic axis, incretin-based therapy has been made available either as injectable GLP-1 analogs (exenatide, liraglutide) or inhibitors of dipeptidyl peptidase-4 (DPP-4), the enzyme responsible for GLP-1 degradation. In clinical trials, when adding exenatide to existing oral antidiabetic therapy, results showed an improvement of ~1% of A1C, in association with a decrease in body weight.

Preliminary studies have suggested concomitant improvements in CV risk factors (HDL, triglyceride, and total cholesterol levels as well as blood pressure) (42). Of interest, experimental data have shown that GLP-1 may enhance recovery of left ventricular function after transient coronary artery occlusion in the isolated rat heart model, possibly due to improved glucose uptake by cardiomyocytes and activation of anti-apoptotic signaling pathways. In the same experimental model, exenatide was shown to reduce post-ischemic infarct size and improve mechanical performance. GLP-1 infusion over 72 h after successful primary coronary intervention in patients with acute myocardial infarction and depressed left ventricular ejection fraction (<40%) was associated with significant improvement in left ventricular ejection fraction (29 ± 2 to 39 ± 2%; $P < 0.01$) and amelioration in global and regional wall motion (43). More recently, the same investigators infused GLP-1 over a 5-week period in patients with advanced heart failure and compared outcomes with those of patients on standard therapy. In the former, left ventricular ejection fraction increased along with $V_{O_{2max}}$ and quality-of-life score. These results suggest that GLP-1 mimetics/analogs may be a suitable candidate in clinical management of diabetic patients with coronary heart disease or heart failure (42). However, more extensive data from clinical trials and judicious postmarketing clinical surveillance are necessary to appropriately evaluate potential CV risk-to-benefit ratio.

Oral inhibitors of DPP-4 increase the plasma concentrations of the biologically active form of endogenously secreted incretins. The first available DPP-4 inhibitor was sitagliptin, followed by vildagliptin, while several others are in the advance stage of clinical development. Clinical studies suggest these agents are safe and tolerable (44). Of interest, the risk for hypoglycemia, a known trigger factor for acute CV events, is very low, whereas body weight neutrality may be of value in overweight/obese type 2 diabetic patients. Beside these nonselective effects, the direct impact of these agents on CV disease is still unknown, but long-term studies are under development to address the issue.

Rimonabant, the first selective endocannabinoid (CB)-1 receptor antagonist, has been extensively investigated in the Rimonabant in Obesity (RIO) program. Rimonabant consistently reduces body

weight, waist circumference, triglycerides, blood pressure, insulin resistance, and C-reactive protein levels and increases HDL cholesterol concentrations in both nondiabetic and type 2 diabetic overweight/obese patients (45,46). However, the drug has been discontinued from the market because of its adverse events.

HYPOGLYCEMIC AGENTS REDUCE CARDIOVASCULAR EVENTS/MORTALITY IN TYPE 2 DIABETES: IS THERE AN AFFIRMATIVE RESPONSE? — Although quickly reviewed, it cannot be denied that the available data are far from providing an evidence-based solid answer to our question. For many of the agents currently in use, randomized controlled trials are not available and when available are limited. Perhaps the best example is metformin. Generally adopted as a preferred first-line (47) treatment, it has been recently proposed that contra-indication to metformin's use should be relaxed to allow more patients to benefit from its multiple effects, including those on CV risk (25). Still, all this is based in a small cohort of the UKPDS (24) including 342 patients (Fig. 1), quite a small sample compared with more recent large-scale trials unable to support clear-cut CV benefit. Even when large trials are available, their interpretation and comparison is not a simple one. Study populations may indeed differ. For instance, while in the UKPDS (1,24), newly diagnosed type 2 diabetic patients with no CV complications were enrolled, and high-risk individuals were included in the University Group Diabetes Project (16) or in the PROactive (31) studies. Treatment of type 2 diabetes has evolved over the time, and it is now widely accepted that multifactorial intervention is required to effectively reduce CV risk, as clearly demonstrated by the Steno 2 study (48). The use of statins and drugs interfering with the renin-angiotensin system, as well as anti-platelet treatment, is nowadays expectedly more common. Because of this, results obtained with a trial performed 10 years ago may not be directly comparable to those concluded today or, even more difficult, to those to be completed tomorrow. Type 2 diabetes is a very heterogeneous chronic condition including young and old individuals, with short or long duration of diabetes, with and without micro- and/or macrovascular complications, with and without comor-
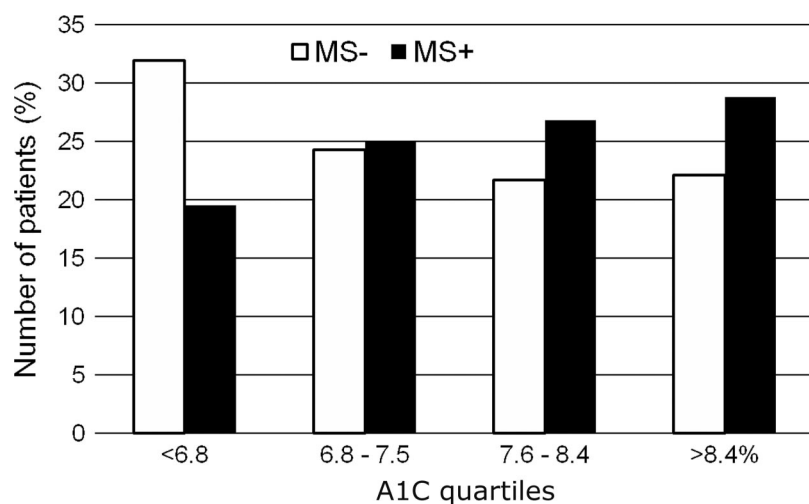
Figure 2—*Prevalence of the metabolic syndrome (MS) (Adult Treatment Panel III criteria) in a population (*n *= 1,610) of type 2 diabetic patients. The presence of the syndrome increases with worsening of glycemic control (A1C). Adapted from Ref. 52.*

bidities not to tell about genetic heterogeneity. In light of such a complex picture, it looks more appropriate that antidiabetic therapy to be individualized with respect to risk-to-benefit ratio. TZDs and CHF is a typical example of the importance of patient selection, highlighting the need for safe procedure as well as safe drugs (37). This becomes even more relevant in light that, due to the chronic and progressive nature of diabetes and the development of the disease at a younger age, multiple hypoglycemic agents will be combined to ensure glycemic control. Even less evaluation is currently available on the multiple permutations that the availability of six classes of oral hypoglycemic agents may generate. Thus, the beneficial effects of metformin shown in the UKPDS were completely lost when the drug was used in combination with sulfonylureas (1), a finding that has been both confirmed and ruled out (49) in subsequent retrospective analysis. In the ACCORD (10), AD-VANCE (11), and VADT (12) trials, treating-to-target required greater exposure to drugs from every class and more frequent changes in the dose or the number of drugs used. Still, the three trials ended up with different results: modest reduction of events with increased mortality in the former in intensively treated diabetic patients. The explanation for excess of mortality in the face of a reduced number of CV events in the ACCORD study remains elusive, but initial analysis could not identify association with any of the oral hypoglycemic agent or combination used. Rather, these trials may return our attention to the value of glycemic con-

trol rather than to the agent(s) used to achieve and maintain it. Although some caution may be warranted in high-risk CV patients in lowering A1C to target values (6.5%) (50), the need for good glycemic control in low-risk patients remains highly recommended (51). Because CV risk is likely to progress with duration of the disease, it is in the early stage of diabetes that strict glycemic control should be attained. Prevention of worsening in glycemic control may also result in an improvement in multiple metabolic alterations. As shown in Fig. 2, the prevalence of metabolic syndrome in type 2 diabetes increases with the worsening of A1C (52). Good glycemic control as represented by A1C levels as close to the normal range from the time of diagnosis has been shown to reduce the risk of microvascular complications—still a major burden to the patient and society (53). With respect to this, it should be kept in mind that diabetic microangiopathy is most likely a diffuse process involving cardiac microcirculation as well affecting coronary reserve, i.e., a main determinant of the post-ischemic necrotic area. Moreover, a typical microangiopathic complication such as diabetic retinopathy is highly predictive of CV outcomes. Maintenance of near-normal glycemic control from the early stage of the disease would require individualized therapies, or at least accurate balance of efficacy and safety of oral hypoglycemic agents. Increasing the availability of such agents, as it occurred in the past few years, will then require a major effort in identifying the most durable form of treatment. If this

could be achieved from the time of diagnosis, then maybe oral hypoglycemic agents will exert their CV protective effect.

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