One hundred million persons have a history of diabetes mellitus (DM) worldwide, 15.7 million reside in the U.S. and conservative estimates suggest that one third of the U.S. diabetic population remains undiagnosed. Furthermore, an additional 40 million persons have insulin resistance syndrome and thus are at heightened risk for developing type 2 DM (1). These numbers are projected to double in the next decade primarily among middle-aged adults, the elderly (2) and, unexpectedly, among children. Although the underpinnings of these epidemiologic observations have yet to be fully realized, there has been a parallel increase in the prevalence of societal obesity (3). Unfortunately, cardiovascular complications remain the leading cause of death among patients with type 2 DM accounting for 70% of all case fatalities. Although there has been a recent decline in the age-adjusted mortality rate among patients with cardiovascular disease, there has not been a coinciding reduction in the adjusted mortality rates among patients with diabetes (4,5) (Fig. 1). Further delineating this heightened risk are data from a Finnish-based population study (6). In this large series, patients with diabetes and history of myocardial infarction (MI) had a yearly vascular event rate (including cardiovascular death, stroke, or MI) of 18.5% which was twofold greater than their nondiabetic counterparts. In fact, patients with diabetes and no prior history of MI had an annual event rate of 1.1%. Similar diabetes nor MI had an annual event rate of 1.1%. Similar data have compelled numerous expert panels, including the Joint National Committee (JNC VI), American Diabetes Association (ADA) and the National Cholesterol Education Program (NCEP), to recommend an aggressive risk factor modification program, with a ratcheting down of traditional risk factors and the early addition of oral antiplatelet therapy.

HYPERGLYCEMIA

Serum glucose level not only defines the onset of diabetes but also is associated with an increased risk of future cardiovascular events among diabetic and nondiabetic patients (10,11) as evidenced by numerous epidemiologic studies (12). Most recently, data from the European Prospective Investigation of Cancer and Nutrition–Norfolk suggest that serum glucose level is associated with an increased risk of death among nondiabetic patients even in the lower quartiles of HgbA1c (13). In this cohort of >4,600 men followed up for four years, there was a graded increase in the Relative Risk of all-cause mortality based on the glyced hemoglobin (<5%, 1.00; 5% to 5.4%, 1.41; 5.5% to 6.9%, 2.07; ≥7%, 2.64; p < 0.001). Excluding patients with diabetes and ischemic heart disease, a 1% increase in the HgbA1c was associated with a relative risk of 1.46 (1.00 to 2.12, p = 0.05) for all-cause mortality. Although there are abundant data linking both fasting glucose and impaired glucose tolerance to adverse events, the data demonstrating an improvement in cardiovascular outcomes with an aggres-
sive glucose lowering treatment strategy have been lacking among patients with type 2 DM. Although data from UK Prospective Diabetes Study (UKPDS)-33 clearly demonstrate a reduction in microvascular complications with intensive glucose control (14), there was not a concomitant significant reduction in macrovascular complications, despite a disproportionate 25% risk of suffering a nonfatal MI or stroke (compared with a 3.4% incidence of developing blindness or 1% incidence of developing renal failure) during a 10-year period.

**INSULIN RESISTANCE**

Insulin resistance precedes the onset of overt hyperglycemia in approximately 80% of patients (15), is a known cardiovascular risk factor, and the definition has recently been clarified by an expert consensus panel. Although the biologic determinants of insulin resistance are varied and remain mostly unexplained, there are emerging mechanisms that have been implicated in the pathophysiology. The insulin receptor gene is located on chromosome 19 and there have been no fewer than 50 mutations in this gene described which, taken in total, cause only rare forms of insulin resistance. However, insulin resistance appears, in part, to be genetically determined. Young, nonobese and glucose-tolerant relatives of patients with type 2 DM have been shown to be insulin resistant (16,17). In fact, approximately 50% of first-degree relatives are insulin-resistant many decades prior to the onset of diabetes (18). The genetic drivers of insulin resistance do not appear to be absolute, as environmental factors are clearly contributory in the development of diabetes. The molecular underpinnings of insulin resistance are not yet defined; nevertheless, there have been numerous agents implicated that are discussed in greater detail later in this work.

The recently updated NCEP guidelines recognize insulin resistance as an important and modifiable cardiovascular risk factor. Insulin resistance, as determined by this expert panel, is present when any three of the following exist in a given patient: a fasting glucose level of >110 mg/dl and <126 mg/dl, elevated triglyceride level >150 mg/dl, central adiposity (abdominal girth >40 in. in men and 35 in. in women), hypertension (>130/>85 mm Hg) and depressed high density lipoprotein (HDL) (<40 mg/dl in men and <50 mg/dl in women) (Table 1). Insulin resistance has been linked to increased production of proinflammatory cytokines and ultimately, to the development of both type 2 DM and atherosclerosis (19–21). In fact, nuclear factor kappa-beta, a key transcription factor responsible for the expression of numerous proinflammatory cytokines, is chronically activated in the peripheral monocytes of patients with type 2 DM, which is distinctly unique compared with circulating monocytes among nondiabetic patients (22).

In addition to diet and exercise, modulation of insulin resistance is currently possible with both metformin and the thiazolidinediones (TZDs). Although the TZDs were initially developed for their antioxidant properties, it became apparent that they had a beneficial effect on serum glucose levels in insulin-resistant animals (23–26). There are currently two agents commercially available in the U.S.: rosiglitazone and pioglitazone. Troglitazone was voluntarily withdrawn from the market, in March of 2000, due to unexpected, severe hepatotoxicity. The TZDs are synthetic...
ligands to a family of nuclear receptors named “peroxisome proliferator-activated receptors” (PPARs). These receptors are members of the steroid/thyroid hormone receptor super family of transcription factors and appear to be important in adipocyte differentiation (27,28). The PPAR family consists of three distinct receptors: PPARα, PPARγ and PPARβ. Once activated, PPAR forms a heterodimer with 9 cis-retinoic acid receptor, binds to deoxyribonucleic acid regulatory regions of target genes, and results in differential gene expression and protein synthesis. The TZDs’ binding affinity for PPARγ appears to correlate with their glucose-lowering ability. The PPARγ are abundantly populated on adipocytes, intestinal cells and macrophages; however, the molecular cascade, linking PPARγ to adipocyte differentiation and insulin resistance, is yet undefined. However, there is mounting evidence that adipocyte-derived hormones may play a key role in the development of obesity and insulin resistance. As these adipocyte-derived hormones have structure homology to cytokines, they are collectively referred to as “adipokines” (29). These identified proteins include tumor necrosis factor-alpha, leptin, adipin, resistin, and adiponectin. In particular, resistin has been linked to the development of insulin resistance in ob/ob and db/db (inherited obesity and diabetes traits) mouse models (30). Adiponectin has been linked with insulin sensitivity in similar diabetic (as well as nondiabetic) mouse models (31,32). Both of these adipokines appear to be modulated by the administration of PPARγ ligands. If the results of these preliminary observations are replicated and the molecular pathways further delineated, modulation of the adipokine axis may prove to offer a new therapeutic strategy for the treatment of obesity, insulin resistance, and type 2 DM.

The glucose-lowering effects of TZDs have been studied extensively in humans. It appears that as a class, they improve glycemic control somewhat less than the sulfonylurea agents or metformin. On average, the fasting plasma glucose level is decreased by approximately 45 mg/dl and the HbA1c by approximately 1% (33,34). The glucose-lowering effects of these agents appear to plateau at doses > 8 mg for rosiglitazone and 45 mg for pioglitazone.

The TZDs have numerous non-glucose-lowering effects that are potentially advantageous. They have a favorable impact on lipoprotein metabolism, fibrinolysis (35), endothelial function, and inflammation. The TZDs may also have antimitogenic properties (36,37). Patients with type 2 DM have a characteristic lipid profile of elevated triglyceride levels, low HDL levels and modestly elevated low density lipoprotein (LDL) levels. As a general rule, the TZD agents increase HDL levels as much as 20% and decrease triglyceride levels, especially when these levels are markedly elevated. Although TZD agents minimally elevate total LDL concentration, they transition small, oxidized LDL particles to larger buoyant, potentially less atherogenic particles (38). Troglitazone has also been demonstrated to result in significant regression of carotid intimal medial wall thickness (39).

However, TZD use can be associated with potentially serious side effects. The development of fluid retention and worsening congestive heart failure symptoms often necessitates the discontinuation of TZD treatment. Thus, these agents are contraindicated in patients with New York Heart Association functional class III to IV symptoms. These agents also can result in significant weight gain. Preclinical studies in a murine model for familial adenomatous polyposis and sporadic colon carcinoma suggested that activation of PPARγ was tumor producing. Thus, TZDs ought not be prescribed to persons with familial adenomatous polyposis coli (40,41).

HYPERTENSION, RENIN-ANGIOTENSIN AXIS, AND DM

Hypertension remains a prevalent and readily modifiable chronic disease. Fifty million Americans have hypertension (42), and the incidence of hypertension is notably increased among patients with dyslipidemia, obesity, and hyperinsulinemia (43). It is estimated that 11 million Americans have both diabetes and hypertension. This “deadly duo” increases the cardiovascular event rate twofold. Furthermore, hypertension among diabetic patients has been linked with numerous other vascular complications such as nephropathy, retinopathy, the development of cerebrovascular disease, and significant decline in cognitive function in middle-aged diabetic hypertensive patients (44).

Recognizing this link between hypertension and diabetes to adverse events, numerous expert panels have recommended lower blood pressure targets for patients with diabetes mellitus (45–47). Prior to substantial efficacy data, the JNC VI recommended a ratcheting down of the target blood pressure among diabetic patients to 130/85 mm Hg (47). The ADA currently recommends a targeted blood pressure of 130/80 mm Hg. This later recommendation has now been validated in two large-scale clinical trials. Both the Hypertension Optimal Treatment (HOT) trial (48) and UKPDS 38 study (49) implemented a multidrug antihypertension regimen, achieved a targeted low blood pressure, and demonstrated improved outcomes among the intensively managed diabetic patients. The HOT trial randomized 1,501 diabetic patients to a diastolic blood pressure of 90, 85 or 80 mm Hg. Based on the HOT trial findings, there were an additional 7.4 lives saved per 1,000 patient years treated in the ≤ 80 mm Hg group. Adopting the more stringent JNC VI guidelines not only seems efficacious but also likely translates into cost savings with an estimated lifetime cost savings of $1,450 (50) (Fig. 2).

Numerous pharmacologic agents have been investigated for the treatment of hypertension among diabetic patients; however, angiotensin-converting enzyme (ACE) inhibitors ought to be considered first-line agents among patients with diabetes. The efficacy was initially established following acute MI (51) with nephropathy (49,52–55) and in the presence of CHF. Both the ABCD and Fosinopril versus Amlodipine Cardiovascular Events randomized Trial
(FACET) (56) trials randomized type 2 DM patients to treatment with either an ACE inhibitor or calcium antagonist. Both studies demonstrated a reduction in cardiovascular events for patients randomized to ACE inhibition therapy. The FACET study randomized patients with diabetes and hypertension to treatment with fosinopril or amlodipine. Although there was a similar reduction in diastolic blood pressure among patients taking both agents, fosinopril treatment was associated with a 50% reduction in cardiovascular events including acute MI, stroke, or angina requiring hospitalization. Although not the primary focus of this trial, these results highlight the importance of ACE inhibition among diabetic patients. The ACE inhibitors have also been shown to attenuate the development of nephropathy and other microvascular complications among patients with either type 1 or type 2 DM (49).

Further extending the efficacy and indications of ACE inhibition among patients with diabetes are MICRO-HOPE data (57). There were 3,577 patients with a reported history of diabetes enrolled in this trial (58). Patients with a history of diabetes were eligible for randomization if they were >55 years and had a history of cardiovascular disease or one other risk factor for heart disease. There was a 25% reduction in MI, stroke or cardiovascular death for the ramipril-treated diabetic cohort (p < 0.001) (Fig. 3A). The mortality rate was 9.7% for the placebo-treated patients compared to the 6.2% for the ramipril-treated patients (p < 0.001) (Fig. 3B). There was also a significant reduction in the rate of MI (12.9% vs. 10.2%, p = 0.01) and stroke (6.1% vs. 4.2%, p = 0.007) for the ramipril-treated diabetic patients compared with placebo-treated diabetic patients.

Although angiotensin receptor blockers (ARBs) have emerged as effective agents in treating hypertension and in prevention of progression of nephropathy among patients with type 2 DM, they should be considered for use only among patients intolerant or allergic to ACE inhibition, given the current breadth of data for ACE inhibitors. The ARBs may offer a more comprehensive inhibition of the

**Figure 2.** This bar graph depicts the lifetime costs associated with the successful implementation of two blood pressure goals. This model was derived using a 60-year-old diabetic hypertensive patient with no prior history of cardiovascular or end-stage renal disease. This figure was adapted with permission from reference 50. ESRD = end-stage renal disease; HF = heart failure; MI = myocardial infarction.

**Figure 3.** The Kaplan-Meier estimates for all-cause mortality for the diabetic patients enrolled in MICRO-HOPE are shown. Figure reproduced with permission from reference 57.
The renin-angiotensin system via inhibition of the angiotensin II tissue receptor, a reduced incidence of hyperkalemia, and no increased incidence of chronic cough associated with long-term usage (59). The results of four large-scale trials confirmed earlier pilot studies suggesting beneficial renal effects of ARBs (Table 2) (60–62). The Reduction of End points in Noninsulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) trials evaluated the efficacy of losartan and irbesartan among patients with type 2 DM with proteinuria and elevated creatinine concentration. Both trials demonstrated a significant reduction in the rate of death, development of end-stage renal disease, or doubling of the serum creatinine concentration with the treatment of losartan or irbesartan. The primary composite end point was 43.5% for the losartan-treated group compared with 47.1% for the placebo-treated group (p = 0.024) in the RENAAL trial. The Irbesartan Microalbuminuria Type 2 Diabetes Mellitus in Hypertensive Patients (IRMA II) and Microalbuminuria Reduction with Valsartan (MARVAL) trials randomized patients with type 2 DM, microalbuminuria and a normal creatinine concentration to irbesartan versus placebo, or valsartan versus amlodipine, respectively. The primary end point in these smaller controlled trials was the development of frank proteinuria. Both of these trials demonstrated significant reduction in the development of proteinuria with ARBs. In the MARVAL trial, 29.9% of valsartan–treated patients returned to normal albuminuric states compared with 14.5% of the amlodipine-treated patients (p = 0.001). Within the MARVAL trial, the baseline urinary albumin excretion rate for the valsartan–treated patients was reduced from 57.97 to 32.3 μg/min. The amlodipine-treated patients’ urinary albumin excretion rate was minimally affected (55.4 to 50.7 μg/min, p < 0.001).

The safety, tolerability and efficacy for beta-blockers among patients with type 2 DM is now established (63,64). In a large series of diabetic patients after an acute MI, there was an approximate 40% reduction in mortality for those patients receiving beta-blockers (64). The 2-year mortality rate was 17% for patients being treated with a beta-blocker compared with 26.6% for those diabetic patients not receiving a beta-blocker (relative risk, 0.64; 95% confidence limits, 0.60 to 0.69). Unfortunately, in this large analysis, only 31% of eligible diabetic patients received treatment with a beta-blocker following infarction. Efficacy of beta-blocker therapy is also evidenced in a study of diabetic patients with known stable coronary artery disease within the Bezafibrate Infarction Prevention trial (65). Within this trial, there was a 44% reduction in the three-year mortality rates for diabetic patients receiving beta-blockers. Treatment with beta-adrenergic antagonists is associated with insulin resistance and impaired lipid metabolism. Unlike selective beta-blockers, carvedilol is a nonselective beta adrenoreceptor and selective alpha adrenoreceptor-blocking agent. Its ratio of beta to alpha blocking potency is 7.6:1. In a small prospective randomized controlled trial of patients with type 2 DM, the efficacy of carvedilol was compared with atenolol (66). The blood pressure and left ventricular mass decreased in both treatment groups; however, carvedilol use was associated with a significant reduction in fasting plasma glucose, insulin and triglyceride levels as well as an increase in HDL cholesterol compared with atenolol. Carvedilol and atenolol are currently being evaluated in a large randomized trial.

**DYSLIPIDEMIA AND DIABETES**

Patients with type 2 DM have a characteristic lipoprotein profile. These patients have a tendency for hypertriglyceridemia, low levels of HDL cholesterol and modestly elevated LDL cholesterol, with a disproportionate elevated level of small-oxidized LDL particles. Both the 4S and Cholesterol And Recurrent Events (CARE) studies have demonstrated a significant reduction in future cardiovascular end points for patients with diabetes and coronary heart disease (CHD) who were with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor. A primary prevention strategy is currently being tested in the Atorvastatin Patients with Non-
Table 3. Order of Priorities for Treatment of Diabetic Dyslipidemia in Adults

<table>
<thead>
<tr>
<th>First choice</th>
<th>Second choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved glycemic control plus high dose statin</td>
<td>Improved glycemic control plus high dose statin plus fibrinolytic agent</td>
</tr>
<tr>
<td>High-dose aspirin</td>
<td>Aspirin plus fibrate</td>
</tr>
<tr>
<td>High-dose clopidogrel</td>
<td>Low-dose aspirin</td>
</tr>
</tbody>
</table>

HDL = high density lipoprotein; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; LDL = low density lipoprotein.

insulin Dependent Diabetes Mellitus (ASPEN) study and the Collaborative Atorvastatin Diabetes Study (CARDS). Additionally, the MRC/BHF Heart Protection Study has currently enrolled 6,000 patients with diabetes; nearly 4,000 of this group do not have a history of CHD (67). These trials will undoubtedly shed important light on the efficacy of utilizing a statin agent for the primary prevention of CHD among diabetic patients. The recent ATP III and ADA recommend a multifaceted lipid-lowering regimen with a targeted LDL of ≤100 mg/dl and considers diabetes as a CHD risk equivalent. Table 3 depicts the current ADA recommendations for the treatment of lipoprotein abnormalities among diabetic patients.

ADJUNCTIVE ORAL ANTIPLATELET THERAPY

Numerous plausible biologic mechanisms have been purported to explain the exceptionally poor outcome of patients with DM and coronary artery disease. Diabetic patients have a propensity for adverse arterial remodeling (68,69), aggressive atherosclerosis (70,71), abnormal endothelial function (72,73), impaired fibrinolysis, platelet hyperactivity and a propensity to form neointima following arterial injury. The diabetic platelet has emerged as a distinct target for therapeutic intervention. Increased platelet activity is certainly involved in the increased thrombogenic potential among diabetic patients. Diabetic platelets are larger, have a greater number of glycoprotein (GP) IIb/IIIa receptors (74) and aggregate more readily to known agonists in vitro than platelets from nondiabetic patients (75). Knobler et al. (76) measured shear-induced whole-blood platelet adhesion and aggregation on the extracellular matrix of diabetic and nondiabetic patients. This ex vivo model more closely approximates the in vivo environment by maintaining the presence of other blood elements, shear force and solid phase subendothelial components. This study demonstrated increased platelet adhesion and aggregation in diabetic patients, which loosely correlated with the degree of dyslipidemia. Furthermore, a greater percentage of diabetic platelets circulate in an activated state.

It is not surprising that diabetic patients derive substantial benefit from aspirin therapy. A meta-analysis from the antiplatelet trialists evaluated the efficacy of aspirin therapy as a secondary preventive strategy. The diabetic substudy in this meta-analysis demonstrated a significant reduction in cardiovascular events for those diabetic patients treated with aspirin. An estimated 38 vascular events were prevented per 1,000 diabetic patients treated (77). Subgroup analysis from the U.S. Physicians Health Study evaluated the efficacy of low-dose aspirin (325 mg, every other day) as a primary prevention strategy (78). Subgroup analysis of this diabetic cohort demonstrated a reduction in the MI rate from 10.2% for the placebo-treated group to 4.0% for the aspirin-treated group. An aggressive antiplatelet strategy for the primary prevention of cardiovascular events is also supported by the Early Treatment Diabetic Retinopathy Study (79). Given these historical data, aspirin administration is requisite among diabetic patients with CHD and seems prudent in patients with type 2 DM at risk for CHD.

Treatment with a thienopyridine may confer additional benefit among diabetic patients with macrovascular disease. The Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events (CAPRIE) trial randomized 19,185 patients with a history of recent stroke, MI, or peripheral arterial disease to treatment with either aspirin or clopidogrel. Overall, there was a modest reduction in the combined event rates of ischemic stroke, MI, or vascular death associated with clopidogrel treatment compared with aspirin therapy, 5.83% vs. 5.32% (p = 0.043), respectively. Substudy analysis of the nearly 4,000 diabetic patients from CAPRIE, randomized to treatment with clopidogrel, demonstrated a significant benefit (80). The annual combined event rate was 17.7% compared with 15.6% (p = 0.042).

ADJUNCTIVE THERAPY DURING PERCUTANEOUS CORONARY INTERVENTION

Diabetic patients undergoing percutaneous coronary intervention (PCI) have numerous high risk clinical and anatomical characteristics and substantially higher rates of late MI, late mortality, and restenosis following PCI. Recent data analyzing over 25,000 patients undergoing PCI suggest that diabetic patients also have an approximate twofold increase in in-hospital mortality, following both elective (1% vs. 2%, p < 0.001) and urgent PCI (6.9% vs. 12.7%, p < 0.001). This increased early hazard for death, following PCI, persisted following multivariable adjustment (odds ratio 1.4, p = 0.04) (81). In addition to aspirin and a thienopyridine, the adjunctive administration of a GP
Ilb/IIIa inhibitor has been associated with an additional reduction in adverse events following PCI.

The early safety and long-term efficacy of abciximab has been extensively evaluated among patients with diabetes undergoing PCI. Of the 2,399 patients randomized within the Evaluation of Platelet Ilb/IIIa Inhibitor for Stenting Trial (EPISTENT), 491 patients had a history of DM and were randomized to treatment with stent-abciximab, stent-placebo, or percutaneous transluminal coronary angioplasty (PTCA)-abciximab (82). The benefit of abciximab therapy among diabetic patients undergoing PCI was apparent at 30 days, persisted through 1-year follow-up, and remained significant following multivariate adjustment. At six months, there was a marked benefit for the stent-abciximab group compared with the stent-placebo and the PTCA-abciximab groups for the combined end point of death, MI, or target vessel revascularization (stent-abciximab, 13.0%; stent-placebo, 25.2%, p < 0.005; PTCA-abciximab, 23.4%). The reduction in this composite was driven by a reduction in all three end points analyzed. The 6-month death or MI rate was 6.2% for the stent-abciximab, 12.7% for the stent-placebo (p = 0.041), and 7.8% for the PTCA-abciximab groups. There was also a significant reduction in the 6-month target vessel revascularization rate for the stent-abciximab-treated diabetic patients (stent-abciximab, 8.1%, stent-placebo, 16.6%, p = 0.021, PTCA-abciximab, 18.4%). Importantly, the efficacy of stent and abciximab was maintained through one-year follow-up (Fig. 4).

The initial findings from EPISTENT have been further substantiated by a pooled analysis from EPIC, EPILOG and EPISTENT (83). The administration of abciximab was associated with a significant reduction in one-year mortality among the 1,462 diabetic patients in these trials (4.5% vs. 2.5%, p = 0.031). The efficacy of abciximab persisted among high risk subgroups of diabetic patients including those with clinical markers of insulin resistance (5.1% vs. 2.3%, p = 0.0044), insulin-requiring diabetic patients (8.1% vs. 6.2%, p = 0.008).

Figure 4. One-year Kaplan-Meier estimates of the invasive treatment arms for the patients with diabetes mellitus enrolled in Evaluation of Platelet Ilb/IIIa Inhibitor for Stenting Trial (EPISTENT) are shown. A = the rate of death or myocardial infarction (MI) within EPISTENT; B = the 1-year target vessel revascularization (TVR) rates. PTCA = percutaneous transluminal coronary angioplasty.
vs. 4.2%, p = 0.073) and those diabetic patients undergoing multivessel intervention (7.7% vs. 0.9%, p = 0.018).

SUMMARY

There remains no doubt that patients with type 2 DM remain at heightened risk for major cardiovascular events in the modern era of medical therapy. It is also clear that these patients derive substantial benefit from current recommendations regarding risk factor modification and available pharmacologic agents. Unfortunately, attaining the recommended risk factor targets and instituting a broad-based pharmacologic treatment strategy has been less than successful (84). Improving the cardiovascular health among patients with diabetes will require a ramping up of societal resources. Focused and effective prevention strategies that are readily applicable across cultures will be key in order to delay and ultimately prevent the onset of type 2 DM. The medical community will need to become engaged with respect to the unique nature of diabetes mellitus and vascular disease and implement broad-based treatment strategies resulting in “poly-pharmacy” of the diabetic person. Lastly, a reinvestment of philanthropy, industry and government-based research resources will be requisite in order to propel our current understanding of the diabetic-vascular axis forward.

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REFERENCES

31. Patel J, Anderson RJ, Rappaport EB. Rosiglitazone monotherapy improves glycaemic control in patients with type 2 diabetes: a twelve-


