

## MANAGING DIABETES MELLITUS IN PATIENTS WITH VASCULAR DISEASES

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**ABSTRACT :** Diabetes mellitus is associated with a markedly increased prevalence of vascular disease. Therefore, management of diabetes mellitus in peripheral arterial disease (PAD) requires multifaceted approach in the form of more vigorous control of hyperglycemia, hyperlipidemia, hypertension, and other risk factors and use of antiplatelet agents.

### INTRODUCTION

Diabetes mellitus is the most common endocrine disease. Type 2 diabetes affects >3% of all adults and >10% of adults >65 years old.<sup>[1]</sup> Eighty percent of patients with type 2 diabetes will die of cardiovascular disease.<sup>[2]</sup>

The risk of vascular diseases is 2-4 times greater in diabetes, occurs at a younger age, and is much higher in women with diabetes. The risk of peripheral arterial disease (PAD) is increased in patients with poor glycemic control, but studies have not shown a major impact of improved glucose management on mortality. This apparent contradiction may be due to the many potential mechanisms of increased cardiovascular damage in diabetes, including hypertension; abnormal clotting function due to changes in fibrinolysis, platelet adherence, and plasminogen activity; abnormal vascular reactivity; and abnormal lipid patterns and particles. Some, but not all, of these issues are related to lifestyle factors, including diet, exercise, and cigarette smoking. The treatment of hypertension and hypercholesterolemia has been more successful in reducing cardiovascular mortality than reducing HbA<sub>1c</sub> levels. One of the major, unresolved questions is whether insulin resistance rather than hyperglycemia is the primary risk factor for cardiovascular disease (CVD).

### (A) GLYCEMIC CONTROL

Serum glucose level not only defines the onset of diabetes but also is associated with an increased risk of future cardiovascular events among diabetic. 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 aggressive 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, there was not a concomitant significant reduction in macrovascular complications.

About 80 % of all diabetic patients have type 2 diabetes mellitus, which characteristically occurs after age 40 years. The metabolic mechanisms of type 2 diabetes are the combination of insulin resistance and a genetically programmed defect in the pancreatic beta-cell secretion of insulin. Although a traditional goal of glycemic control in the treatment of diabetes mellitus is to normalize fasting plasma glucose, emerging data indicate that modulation of postprandial plasma glucose levels plays an important role in overall glycemic control. The glycemic threshold for the

development of macrovascular complications is lower than that for microvascular complications, so there is more evidence for an association with postprandial glycemia. Postprandial glucose elevations are associated with postprandial hyperinsulinemia and higher plasma levels of triglycerides, chylomicrons, chylomicron remnants, and free fatty acids. High concentrations of free fatty acids have been associated with endothelial dysfunction,<sup>[6]</sup> and high triglyceride levels have been linked to low levels of high-density lipoprotein (HDL) cholesterol and a preponderance of small, dense, low-density lipoprotein (LDL) particles. Associated with carotid artery atherosclerosis in nonobese white subjects. In addition, high postprandial glucose levels result in protein and cellular glycosylation. Glycosylated LDL particles are more easily oxidized and taken up by macrophages through the scavenger receptor. This, in turn, leads to higher foam cell production, and, ultimately, atherosclerotic plaque. In addition, glycosylated LDL also stimulates platelet aggregation. Glycosylated HDL is less efficient than nonglycosylated in transporting cholesterol back to the liver for metabolism. Additionally, the formation of advanced glycosylated end products in the collagen of the vessel wall itself may directly stimulate or accelerate the atherosclerotic process.

Acute increases in plasma glucose also stimulate the production of free radicals, another factor involved in the atherosclerotic process.<sup>[9]</sup> Excessive postprandial plasma glucose levels have also been associated with transient hypercoagulability resulting from increased thrombin production and decreased fibrinogen breakdown. These, in turn, result from the overproduction of plasminogen activator inhibitor, which directly inhibits tissue plasminogen activator activity. Control of postprandial hyperglycemia reverses this hypercoagulable state.

Endothelial dysfunction is another consequence of postprandial hyperglycemia. Activation of protein kinase C in the endothelium increases adhesion molecules that facilitate leukocyte uptake into the blood vessel wall; increases production of the vasodilators nitric oxide and prostaglandin; increases expression of the vasoconstrictor endothelin; and induces platelet aggregation.

The standards of care in patients with diabetes (American diabetes Association) are preprandial glucose levels of 80 to 120, time glucose levels of 100 to 140, and hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) below 7 percent. The ADA recently (January 2004) recommended lowering the upper limit for normal fasting glucose (NFG) from 110 mg/dL to 100 mg/dL (Table 1) and designating the category of IFG to be at 100-125 mg/dL rather than 110-125 mg/dL.<sup>[13]</sup> The basis for this recommendation was that the threshold of FPG, above which risk of a clinical or metabolic outcome rises sharply, was lower than 110 mg/dL. Plasma HbA<sub>1c</sub> reflects the average glucose level of the previous weeks and allows a uniform measure for achieving a target as well as comparing the efficacies of different therapies.

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**Table 1. Treatment Goals for Type 2 Diabetes**

Parameter	Therapeutic Goal
Body mass index	< 25 kg/m <sup>2</sup>
Blood pressure	< 130/85 mm Hg
Plasma glucose	
Fasting	80 - 100 mg/dL
Postprandial (2 h)	< 160 mg/dL
HbA <sub>1c</sub>	< 7%
Total cholesterol	< 200 mg/dL
HDL-C	>50 mg/dL
LDL-C	d <sup>n</sup> 100 mg/dL
Triglycerides	< 150 mg/dL

## MEASURES TO CONTROL HYPERGLYCEMIA

### Lifestyle intervention

**Diet** since more than 80% of patients with type 2 diabetes are overweight, initial intervention mostly centers around dietary control and increased aerobic exercise.

**Obesity** has a demonstrated association with coronary heart disease. Numerous studies have shown an increased mortality rate in individuals with a BMI of at least 30. These individuals have a 50% to 100% increased risk of death from all causes compared with individuals at a BMI of 20 to 25. Weight loss of at least 7% of current body weight should be an initial goal, since this will produce significant metabolic improvement in glucose control and other associated risk factors, including blood pressure and dyslipidemia.

**Cigarette smoking** is a powerful predictor of mortality. Multiple large prospective cohort studies have demonstrated a 2-fold increase in the relative risk for all-cause mortality in smoking versus nonsmoking diabetic patients, and it has been calculated that the benefit of smoking cessation is the most cost-effective risk factor intervention for diabetic patients.

**Exercise** for 30-60 minutes of moderate-intensity activity 4-5 times weekly (walking, jogging, cycling). Increased in daily lifestyle activities (Stairs, gardening, household chores) is recommended by ADA. Particular emphasis on patients with hypertension, elevated triglyceride, elevated glucose levels.

### Oral Hypoglycemic Agents (table 2)

**Sulfonylureas** are the typical therapy for lean patients with type 2 diabetes and are used in combinations with other agents in obese type 2 patients. Sulfonylureas bind to a receptor on the beta cells and inhibit the sodium-adenosine triphosphate (Na-ATP) channel and increase in intracellular calcium results in insulin exocytosis. Some experts point to a possible risk of increased myocardial damage in patients with known CAD or PAD who use sulfonylureas at the time of an ischemic event. Prevention of protective ischemic preconditioning of the heart by inhibition of the potassium (K)-ATP channel is the putative mechanism. The UKPDS data do not support this concern. Therefore use of sulfonylureas in appropriate patients with PAD.

**Repaglinide** newer insulin secretagogue binds to a different receptor site than the sulfonylureas on the K-ATP channel. 166 The half-life of this drug is 3.7 h, which makes it effective for postprandial rather than preprandial hyperglycemia, for use in the elderly and for diabetic patients with chronic renal failure.

**Metformin** is a biguanide drug that has main mode of action is

**Table 2. Oral Drugs Currently Available for the Treatment of Type 2 Diabetes**

Drug Class	Primary Mechanism	Potential Secondary Benefit	Potential Problems	Main Contraindications
Sulfonylureas/Meglitinides (repaglinide)	Augmented insulin secretion	More rapid onset of action	Weight gain, hypoglycemia	Hepatic disease
Biguanides (metformin)	Reduced hepatic glucose production	Reduction in lipids, less weight gain	Gastrointestinal side effects	Renal insufficiency, CHF
Thiazolidinediones	Enhanced insulin sensitivity	Reduced circulating insulin levels, possible beta-cell preservation and vascular protection	Hepatotoxicity, fluid retention, weight gain	Abnormal liver function, CHF
Acarbose	Delayed gut absorption of carbohydrates	Rare systemic effects	Flatulence	Gastrointestinal disease

through decreasing hepatic glucose output primarily by inhibiting gluconeogenesis, typically without hypoglycemia. Metformin is effective alone or in combination with insulin, sulfonylureas, and thiazolidinediones. The drug usually results in weight loss as a result of decreased appetite for up to 1 year after the initiation of the therapy.

Significant decreases in LDL cholesterol and triglycerides occur. The incidence of lactic acidosis with metformin is 9 per 100,000 person-years. Contraindications to its use include an elevated creatinine level (>1.4 in women, >1.5 in men), congestive heart failure, severe pulmonary disease, or any hypoxic state.

**Thiazolidinediones** promote insulin-stimulated glucose transport in muscles and adipocytes through a mechanism of action involving activating peroxisome proliferators activated receptor-gamma (PPAR- $\gamma$ ) ligands. Binding to the nuclear receptor promotes differentiation of adipocytes and increased expression of glucose transporter. Thiazolidinediones also may act by antagonizing the effects of cytokines such as TNF- $\alpha$ .

Endogenous C peptide is necessary for all the thiazolidinediones to be effective when used in combination with insulin. These agents can result in a reduction from two injections of insulin a day to one. The Thiazolidinediones are associated with weight gain partly resulting from improvement in glycemic control.

**Rosiglitazone** monotherapy results in a decrease of Hb A<sub>1c</sub> of 0.8 to 1.5 percent greater than that seen with placebo, with the greatest reduction seen when it was given in two divided doses. 184, 185 Combination studies of rosiglitazone with metformin for 26 weeks resulted in a 1.0- to 1.2-percent placebo-adjusted decrease in Hb A<sub>1c</sub>. 186 Although rosiglitazone is currently approved for use as monotherapy and in combination therapy with metformin, it also is expected to be efficacious with sulfonylureas or insulin. Rosiglitazone has been reported to result in an increase in LDL and HDL cholesterol concentrations between 12 and 19 percent, with changes in serum triglycerides similar to those seen with placebo.

**Pioglitazone**, the newest thiazolidinedione, has been approved for use as monotherapy and in combination with metformins, sulfonylureas, and insulin. In three randomized, double-blind placebo-controlled trials of 16 to 26 weeks duration, changes in Hb A<sub>1c</sub> were 1.0 to 1.4 percent. 188 Increases in alanine aminotransferase (ALT) occurred in 0.26 percent of treated patients, a result that was not different from that with placebo. 188 Patients treated with pioglitazone showed a decrease in serum triglyceride (9.3 to 9.6 percent), increases in LDL (5.2 to 6.0 percent) with the 30- to 45-mg doses respectively.

Table 3. Pharmacologic Effects of Thiazolidinediones

• Improved glycemic control in type 2 diabetes patients and animal models by reduction of insulin resistance in muscle, liver, and adipose tissue
• Stimulation of differentiation and fat metabolism predominantly in subcutaneous adipose tissue depots +Reduction in circulating triglyceride and free fatty acid levels
• Reduction in circulating insulin and glucose levels
• Increased expression of glucose transporter molecules in insulin target tissues
• Reduction in proportion of atherogenic small, dense LDL-C particles
• Preservation of pancreatic $\beta$ -cell mass (animal studies)
• Reversal of effects of tumor necrosis factor- $\alpha$ , which inhibits insulin action in target tissues (animal studies)

### Insulin

The natural history of type 2 diabetes is one of progressive  $\beta$ -cell failure. Therefore, after approximately 10 years of the use of oral hypoglycemic agents, insulin will be required either in combination with oral agents or as the sole therapy. Although endogenous hyperinsulinemia is clearly associated with atherogenesis, there is no compelling evidence of increased risk of cardiovascular disease or increased mortality from exogenous insulin therapy.

*Treatment Modalities* that enhance insulin sensitivity

- Diet (caloric restriction)
- Weight loss if obese
- Aerobic exercise
- Thiazolidinediones
- Metformin

On one hand, fast-acting and regular insulin are absorbed too slowly to reproduce the typical secretory burst of native circulating insulin, whereas long-acting insulins, like Lente and NPH, are absorbed too rapidly to simulate a normal pattern of basal insulin secretion.

The advent of recombinant DNA technology has led to the development of novel insulin molecules with absorption and biological activity profiles that more closely resemble the physiologic pattern of insulin secretion.

This has, in part, been made possible by the recent development of insulin analogues that target both postprandial blood glucose excursions (rapid-acting analogues) and basal glucose levels (long-acting analogues). The analogues can provide better physiologic control of glycemia throughout the day with a lower incidence of hypoglycemic events than subcutaneously injected native human insulin.

*Rapid-Acting Insulin Analogues* Insulin lispro and insulin aspart are the 2 available rapid-acting insulin analogues. They have a shorter time to onset and shorter duration of action than regular human insulin. These analogues begin to work within 5-15 minutes of injection, achieve peak activity in about 60-90 minutes, and have a duration of action of approximately 4 hours. They are absorbed from the injection site twice as fast as is regular insulin, which begins to act 30 minutes after injection, reaches its peak at 2-4 hours, and lasts 6-8 hours or longer. These characteristics allow patients to administer rapid-acting insulins immediately before mealtime, providing more flexibility in scheduling mealtimes and better control of postprandial glucose levels. In

addition to achieving lower postprandial blood glucose at 1 and 2 hours after meals, rapid-acting insulin analogues maintain the same time-action profile regardless of dose, whereas a dose increase with human regular insulin increases the duration of action.

Insulin lispro has been shown to improve postprandial glucose control without increasing the risk for hypoglycemia in patients with type 1 and type 2 diabetes. Several studies on patients with type 1 diabetes show improvement in levels of HbA1c, ranging from 0.3% to 0.5% reductions in those receiving insulin lispro compared with those receiving regular human insulin, with no increase in the rate of hypoglycemia. Insulin lispro is also associated with a lower risk for severe hypoglycemia and coma. As part of a basal-bolus regimen with NPH, insulin lispro was associated with a lower incidence of nocturnal hypoglycemia than was regular insulin in patients with type 1 diabetes who maintain tight glycemic control. In patients with type 2 diabetes, the addition of lispro to a sulfonylurea has been shown to significantly reduce fasting and postprandial glucose concentrations as well as HbA1c values compared with sulfonylurea alone or sulfonylurea plus either metformin or bedtime NPH.

Similarly, studies show a significant reduction in HbA1c levels in patients receiving continuous subcutaneous insulin infusion (CSII) with insulin lispro compared with patients receiving pump treatment with regular human insulin.

Studies comparing insulin aspart with regular human insulin in patients with type 1 diabetes indicate that aspart improves postprandial glycemic control and reduces the number of hypoglycemic episodes requiring third-party intervention. A recent study by Raskin and colleagues showed that patients assigned to the insulin aspart group experienced a modest but significant reduction in HbA1c at 6 and 12 months of the study when compared with patients in the regular human insulin group.

*Long-Acting Insulin Analogues* NPH and Lente (insulin zinc) are intermediate-acting insulins that are twice as slow as regular insulin with an onset of action of 1-2 hours; NPH insulin exhibits a peak activity of 4-10 hours and a duration of 10-16 hours, whereas Lente peaks at 4-12 hours and lasts for 12-18 hours. Ultralente insulin is a long-acting insulin formulation that has a modest peak at 10 hours and duration of 18-20 hours. Ultralente insulin, however, varies greatly in its absorption characteristics from day to day. Glargine is a long-acting insulin analogue that has a flat, peakless profile of activity that lasts for more than 24 hours in most patients.

*Premixed Insulin Formulations* have the advantage of providing more convenience and greater accuracy for patients because the patient does not need to mix them. The premixed insulin formulations currently available for use are a combination of NPH and regular insulin (70/30 mixture or 50/50 mixture) and a combination of 75% neutral protamine lispro (NPL) and 25% insulin lispro (insulin lispro mixture 75/25). Insulin lispro mixture 75/25 has been shown to be more effective in reducing morning and evening postprandial glucose excursions [41] and in reducing nocturnal hypoglycemia than the NPH/regular insulin 70/30 mixture.

### (B) TREATMENT OF HYPERTENSION

Hypertension (defined as a blood pressure 140/90 mmHg) is an extremely common co morbid condition in diabetes, affecting 20-

60% of patients with diabetes, depending on obesity, ethnicity, and age. In type 2 diabetes, hypertension is often present as part of the metabolic syndrome of insulin resistance also including central obesity and dyslipidemia.

Aggressive blood pressure control prevents further cardiovascular events more in diabetics than in nondiabetics. The ADA currently recommends a targeted blood pressure of 130/80 mm Hg.

#### (C) TREATMENT OF DYSLIPEDEMIC

The most common pattern of dyslipidemia in patients with type 2 diabetes is elevated triglyceride levels and decreased HDL cholesterol levels. The mean concentration of LDL cholesterol in those with type 2 diabetes is not significantly different from that in those individuals who do not have diabetes. However, qualitative changes in LDL cholesterol may be present. In particular, patients with diabetes tend to have a higher proportion of smaller and denser LDL particles, which are more susceptible to oxidation and may thereby increase the risk of cardiovascular events.

Life style modification should be the first step to improve lipid profile, followed by strict glycemic control which lessens hepatic VLDL production.

*Statins* (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor) are first-line agents for decreasing LDL cholesterol, but they also lower the apo B-containing lipoproteins, including atherogenic TGRLP or remnant lipoproteins. These agents result in a proportionately greater cardiovascular risk reduction in diabetic than in non diabetic subjects.

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 PAD. In Heart Protection Study (HPS), which included 5963 subjects with diabetes, simvastatin decreased the risk of coronary death, non fatal myocardial infarction, stroke or revascularization by 25% in the diabetic group with PAD. The reduction risk even extended to patients with pretreatment LDL cholesterol levels below 100 mg/dl.

*Fibrate*, agonists of peroxisome proliferator-activated receptor-alpha (PPAR-alpha), modulate the expression of key genes involved in lipid transport and metabolism in liver and adipose tissue. These alterations result in reduced production of hepatic TG-rich lipoproteins, enhanced TG clearance, and increased HDL-C production of particles. The effect of fibrate therapy on the lipid and lipoprotein profile is characterized by elevation of HDL-C levels ranging from +5% to +20%, mean reduction in TG-rich lipoproteins ranging between 20% and 55%, and a shift in the dense LDL phenotype to receptor-active, buoyant LDL. Fibrates reduce triglyceride levels most effectively in patients with the highest levels. Several diabetes subgroup analyses from primary and secondary CHD prevention trials compared fibrate therapy with placebo; of these, the VA-HIT trial showed a significant CHD reduction of 24%, while the results of DAIS and the diabetes subgroup in the HHS were not statistically significant. In the Bezafibrate Infarction Prevention (BIP) study, which included 330 subjects (11%) with diabetes and 293 patients (9%) with IFG levels at baseline, the primary end point was fatal MI, nonfatal MI, or sudden death with secondary end points included hospitalization for unstable angina, percutaneous transluminal coronary angioplasty, and coronary artery bypass grafting. Bezafibrate

therapy raised HDL-C by 18%. Patients with diabetes mellitus and IFG, both at baseline or diagnosed during follow-up, had a significantly higher rate of secondary end points than patients with NFG ( $P < 0.0001$ ). Bezafibrate treatment reduced secondary end points only in patients with NFG ( $P = 0.04$ ). Thus, diabetes mellitus and IFG were predictive of a worse clinical outcome that was not attenuated with bezafibrate treatment.

The combination of a fibrate with statin therapy was evaluated by Wiklund and colleagues who compared the effects of gemfibrozil 1200 mg, pravastatin 40 mg, pravastatin plus gemfibrozil, or placebo in a 12-week randomized, controlled trial in 290 patients with total cholesterol greater than 232 mg/dL and TGs less than 354 mg/dL. Gemfibrozil plus pravastatin produced a 17% increase in HDL-C compared with a 6% increase by pravastatin alone and a 15% increase by gemfibrozil alone. The incidence of myopathy associated with statin therapy is increased when statins are used in combination with agents such as fibric acid derivatives that share common metabolic pathways.

#### (D) ANTIPLATELET THERAPY

Platelets play a major role in the ischemic manifestations of PAD. Patient with diabetes have a "prothrombotic" state which is characterized by the constellation of endothelial dysfunction, increased platelet adhesiveness and exaggerated platelet aggregation, ultimately resulting in intraluminal thrombus formation. In this milieu of "diabetic heightened platelet activity", therapy with antiplatelet agents is, therefore, expected to confer significant beneficial effects in reducing cardiovascular events.

##### Antiplatelet Therapy in Secondary Prevention of Cardiovascular Events in Patients With Diabetes & PAD

Diabetic patients with prior vascular disease are at a high risk for recurrent cardiovascular events and, in the absence of any absolute contraindication, should be treated with aspirin. In the CAPRIE (Clopidogrel versus Aspirin at Risk of Ischemic Events) trial of 19,185 patients with atherosclerotic vascular disease, clopidogrel (75 mg daily) was superior to aspirin (325 mg daily) in reducing the risk of MI, ischemic stroke or vascular death.[88] The rate of vascular events per year was 15.6% in the 1,914 diabetic patients randomized to clopidogrel and 17.7% in the 1,952 diabetic patients randomized to aspirin ( $p = 0.042$ ); in the nondiabetic patients, the event rates per year were 11.8% and 12.7%, respectively ( $p = 0.096$ ). It was concluded that clopidogrel is especially potent in reducing the elevated risk for recurrent ischemic events in diabetic patients with a prior history of vascular disease. In the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial, the effect of combination therapy with aspirin plus clopidogrel, versus aspirin alone, was evaluated in the 12,562 patients with non-ST elevation ACS. The primary composite outcome of death, nonfatal MI or stroke occurred in 9.3% of the aspirin plus clopidogrel group and in 11.4% of the aspirin alone group ( $p < 0.001$ ). Although a specific analysis of the diabetic subgroup is not available, the combination of aspirin plus clopidogrel reduced the risk of composite endpoints from 16.7% to 14.2%, pointing out the potential efficacy of this regimen in diabetic patients.

#### CONCLUSION

Peripheral Vascular Disease is should be evaluated at least in part by their

effect on cardiovascular effect. Although there are no studies available to directly suggest beneficial effect of blood glucose control on macrovascular effect yet, present data strongly indicate tight glycaemic control of both fasting and postprandial glucose level is of help to achieve this goal. Glycaemic control can be achieved with lifestyle intervention, oral hypoglycaemic effect mainly metformin, thiazolidinediones which have properties that may be associated with cardiovascular disease benefit in the long run and recently available newer insulin analog. Use of ACEI or ARB should get precedence over others agents apart from optimum utilization of beta blocker for aggressive blood pressure control to currently recommended targeted level of 130/80 mm Hg. Although reduction of low-density lipoprotein cholesterol is the primary target of treatment to reduce the risk of cardiovascular events, including stroke reduction of elevated triglyceride levels is now considered a secondary target for risk reduction. Lower goals for triglycerides — including normal levels at <150 mg/dL — have also been set for triglyceride therapy. Dietary modifications and increased exercise remain the initial therapeutic approaches; however, pharmacologic intervention may be required for many patients. Selection of the appropriate agent from among the available medications, including statins, fibrates, nicotinic acid, and omega-3 fatty acids, depends on the degree of triglyceride elevation and the presence of other lipoprotein abnormalities. Platelet inhibition with oral or intravenous agents has “normalized” the increased risk of diabetic patients with PAD. Aspirin is effective in the primary prevention of fatal and nonfatal MI in patients with diabetes, and in the absence of contraindications, should be given to all diabetic subjects at high risk for vascular disease. Clopidogrel has been proven superior to aspirin, especially in diabetic patients.

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