Insulin Resistance and Cardiovascular Disease: New Perspectives From Vascular Biology
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Cardiovascular Disease and Insulin Resistance: Challenges and Opportunities
The Behavioral Risk Factor Surveillance System (BRFSS) is an annual, state-wide telephone survey of randomly selected households. Reeves et al used BRFSS data from 153,805 respondents, ages 18 to 74 years, surveyed in 2000.\(^1\)

In all, 24% to 78% of respondents smoked, had a body mass index (BMI) \(\geq 25\) kg/m\(^2\), did not consume fruits and vegetables regularly, or did not engage in physical activity of moderate intensity on a regular basis.

The data illustrate that the majority of Americans do not follow a healthy lifestyle. In contrast, only 16.8% of respondents (data not shown) included all four healthy lifestyle characteristics in their lifestyles:

- Nonsmoking
- Healthy weight (BMI \(\leq 25\) kg/m\(^2\))
- Regular consumption of fruits and vegetables (\(\geq 5\) times daily)
- Regular exercise (\(\geq 5\) times weekly)

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• As shown previously, most Americans are sedentary and do not eat a healthy diet, suggesting that the prevalence of type 2 diabetes will continue to rise.

• Most recent estimates (2002 data) suggest that there are 13.9 million Americans with diagnosed diabetes.¹

• Wild et al have projected that this number will rise to 30.3 million by 2030—a 118% increase.²

• With numbers this large, all communities—and in particular, cardiology practices in these communities—are likely to be affected.


Unadjusted estimated prevalence data from the January to September 2004 National Health Interview Survey indicate the prevalence of both obesity and diabetes appear to have grown at comparable rates since 1997, illustrating that obesity is an important risk factor for the development of diabetes.¹

• Narayan et al estimated the lifetime risk of diabetes based on data from the National Health Interview Survey (1984–2000).\(^1\)

• The slide shows the estimated proportion of individuals who will develop diabetes by various ages. The investigators found that 32.8% of males (or 1 in 3) and 38.5% of females (or 2 in 5) born in 2000 will eventually develop diabetes. This lifetime risk of diabetes is comparable to that associated with other chronic conditions such as hypertension and coronary heart disease.

• Importantly, the risk is even higher among minorities:
  - 40.2% of non-Hispanic black males and 49% of non-Hispanic black females
  - 45.4% of Hispanic males and 52.5% of Hispanic females

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• Savage et al analyzed data from 1912 adults with diagnosed coronary artery disease (CAD) who had entered cardiac rehabilitation programs in Burlington, VT, and Boston, Mass.\(^1\)
  o 50% of these individuals had the insulin resistance syndrome.

• Milani et al analyzed data from 235 adults with a recent coronary event who had entered a cardiac rehabilitation program in New Orleans, La.\(^2\)
  o 58% had the insulin resistance syndrome.

• Finally, Curran et al studied 85 young adults (ages <45 years) presenting with acute myocardial infarction (MI).\(^3\)
  o 58% had the insulin resistance syndrome.
  o The investigators concluded that the insulin resistance syndrome is an underrecognized risk factor for MI in younger adults.

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• Norhammar et al assessed glucose metabolism in 181 consecutive patients admitted to the coronary care units of two Swedish hospitals with acute MI.¹

• All subjects had blood glucose levels <200 mg/dL and were free from a history of diabetes.

• Investigators administered a standard oral glucose tolerance test at discharge and 3 months later.

• Results of the 3-month test:
  o 35% had impaired glucose tolerance (IGT) (2-h glucose levels 144–199 mg/dL).
  o 31% had diabetes (2-h glucose level ≥200 mg/dL).

• In summary, the data indicate a high prevalence of abnormal glucose metabolism in CAD patients.

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• The metabolic derangements of an obese lifestyle result in a state of chronic inflammation and oxidative stress and, ultimately, insulin resistance.¹

Elevated glucose increases risk in elderly patients with acute MI

Kosiborod M et al. 
Circulation. 2005;111:3078-86.

Kosiborod et al conducted a retrospective analysis of data from the Cooperative Cardiovascular Project, a national program developed by the Centers for Medicare and Medicaid Services. They selected a national sample of 141,680 patients age ≥65 years hospitalized with acute MI between 1994 and 1996.

The slide shows crude 30-day mortality in patients with and without a history of diabetes, and further classified according to glucose level at hospital admission.

- In patients without diabetes, the mortality risk increased as admission glucose became greater. Investigators hypothesize that many of this subgroup had undiagnosed diabetes.
- In contrast, in the subgroup with a history of diabetes, a glucose-associated increase in mortality risk was seen only in severe hyperglycemia.

Investigators concluded that elevated glucose is common in elderly patients with acute MI. The data are consistent with studies in other populations and suggest that strict glucose control may improve outcomes in acute MI.

In conclusion, evidence suggests the components of the insulin resistance syndrome interact to place patients at high global risk for CV events.

• Quiñones et al assessed coronary blood flow response to the cold pressor test (measured by endothelium-dependent vasodilation) in 50 insulin-resistant and 22 insulin-sensitive Mexican Americans. Patients with hypertension were excluded from the study.

• Insulin sensitivity was measured using a euglycemic hyperinsulinemic clamp. A steady-state glucose infusion ≤4.0 mg/kg identified insulin-resistant subjects, and ≥7.5 mg/kg identified insulin-sensitive subjects.

• Myocardial blood flow (MBF) response to dipyridamole infusion (which causes endothelium-independent vasodilation) was similar in both groups.

• The investigators concluded that insulin resistance is associated with endothelial dysfunction in patients without hypertension, dyslipidemia, or IFG.

Mean baseline values

<table>
<thead>
<tr>
<th></th>
<th>Insulin sensitive</th>
<th>Insulin resistant</th>
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<tbody>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>88.9</td>
<td>96.2</td>
</tr>
<tr>
<td>Total-C</td>
<td>167</td>
<td>175</td>
</tr>
<tr>
<td>HDL-C</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>78</td>
<td>139</td>
</tr>
<tr>
<td>Myocardial blood flow</td>
<td>↑ 47.6%</td>
<td>↑ 14.4%</td>
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<tr>
<td>(P = 0.003)</td>
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• Prior and colleagues\(^1\) extended the work of Quiñones et al\(^2\) by assessing endothelial function over the spectrum of insulin resistance.

• MBF response to the cold pressor test was measured in insulin-sensitive subjects (n = 19) and in subjects with insulin resistance (n = 47), impaired glucose tolerance (n = 25), diabetes (n = 21), and diabetes plus hypertension (n = 8). Insulin sensitivity was measured in the same manner as the study by Quiñones et al.\(^2\)

• MBF increased by 44%, 14%, 7%, and 10% in the insulin-sensitive, insulin-resistant, impaired glucose tolerant, and diabetes groups, respectively.

• MBF changed by –2% in the group with diabetes plus hypertension.

• Taken together, these two studies indicate that endothelial dysfunction is present in the early stages of insulin resistance and becomes progressively worse as glucose intolerance develops.

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• Leoncini et al studied the association of the insulin resistance syndrome and target organ damage in 354 adults (mean age 47 years) with untreated hypertension. The investigators used modified ATP III criteria, replacing waist circumference with BMI.

• Microalbuminuria was defined as an albumin-to-creatinine ratio 2.38 to 19 mg/mmol (men) and 2.96 to 20 mg/mmol (women). Left ventricular (LV) hypertrophy was defined as an LV mass index >51 g/m² in both men and women.

• There was significantly higher prevalence of microalbuminuria (P = 0.04) and LV hypertrophy (P = 0.003) in subjects with the insulin resistance syndrome compared to those without the metabolic syndrome.

• Thus, subclinical as well as clinical cardiovascular (CV) disease appears to be accelerated in persons with the insulin resistance syndrome.

• Chronically elevated levels of insulin, glucose, and lipids, along with decreased levels of the adipokine adiponectin, lead to pancreatic β-cell failure, alterations in lipoprotein structure and function, hypertension, inflammation, and a prothrombotic state.

• Increasing insulin sensitivity is a potentially important strategy for addressing these pathologic changes.
New perspectives in cardioprotection: Focus on PPARγ activation
Potential role of PPAR activation in CV risk reduction

- Peroxisome proliferator-activated receptors (PPARs) are a family of steroid hormone nuclear receptors that, when activated, beneficially regulate a number of metabolic processes.\(^1\)

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Three isotypes of PPARs have been identified: PPARα, PPARγ, and PPARδ.

When activated (by ligand binding), they act as transcription factors regulating glucose metabolism and inflammation.\(^1\)

PPARα activation with agents such as fibrates primarily enhances free fatty acid (FFA) oxidation and controls expression of genes regulating lipoprotein concentrations.\(^2\)

PPARδ activation appears to be involved in wound closure and myelination, although less is known about this PPAR subtype than the other two.\(^2\)

PPARγ activation is currently the subject of intensive research and the focus of this slide kit.

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• The anti-inflammatory effects of PPAR activation are hypothesized to be a new approach to blunting atherosclerosis. Direct effects on the vascular wall as well as indirect effects of improving glucose and lipid metabolism are mediated via adipocytes and other peripheral tissue.¹

This slide kit focuses on the implications of PPARγ activation with agents such as the thiazolidinediones. Effects include improving insulin sensitivity and preserving pancreatic β-cell function, as well as improvements in a number of traditional and new CV risk factors.1

• Two thiazolidinediones are currently approved for glucose control in this country: pioglitazone and rosiglitazone. A third, troglitazone, was withdrawn from the market in 2000.

• Numerous clinical and experimental studies of these agents have been published in the past 5 years. Examples of major findings are discussed herein. Agents with combined PPARα/γ activity are in Phase III clinical trials.

• Other treatment options are currently in development.¹

• The effects of PPAR modulation on glucotoxicity are discussed in the next slides.
Insulin resistance may impair β-cell function through the adverse effects associated with elevated blood glucose (a phenomenon known as glucotoxicity) or free fatty acids (a phenomenon known as lipotoxicity).\textsuperscript{1,2}

Elevated free fatty acids may also form a feedback loop, causing or worsening insulin resistance.\textsuperscript{1}

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Clinical evidence that β-cell failure was not preprogrammed, but was related to chronic insulin resistance came initially from the Troglitazone in Prevention of Diabetes (TRIPOD) study. The main findings are summarized on this slide.

• The Diabetes Prevention Program Research Group reported on the association of insulin sensitivity and secretion and incident diabetes.¹

• As shown, subjects with the lowest baseline levels of insulin sensitivity or secretion were at highest risk for progression to diabetes. These findings support the hypothesis that reduction in both insulin sensitivity and insulin secretion (ie, β-cell function) contribute to incident diabetes.

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• The Diabetes Prevention Program (DPP) confirms the TRIPOD results in prevention of new-onset diabetes.¹

• The 2343 subjects at high-risk of diabetes, as measured by elevated fasting and postload glucose concentrations, were randomized to troglitazone 400 mg, metformin 850 mg bid, intensive lifestyle modification (≥7% weight loss plus ≥150 min/wk physical activity), or placebo.

• The slide summarizes cumulative incidence of diabetes by subgroup for the 1.5 years before early termination of the troglitazone arm (concerns of possible liver toxicity):
  o Troglitazone (n = 585), metformin (n = 587), lifestyle intervention (n = 589), and placebo (n = 582)

• Compared with placebo, troglitazone reduced the development of diabetes by 75%, lifestyle intervention by 58%, and metformin by 44%.

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• Confirmation of the TRIPOD and DPP findings comes from a study by Ovalle and Bell, who randomized 17 subjects with type 2 diabetes to insulin or rosiglitazone 8 mg once daily for 6 months.1 All subjects had glucose inadequately controlled on maximal doses of glimepiride and metformin.

• A1C levels in the two groups were well matched at baseline and a study end.

• After 6 months, there was a significant improvement in β-cell function in the thiazolidinedione group, as evidenced by a restoration of the acute-phase insulin response to glucose (AIRg, measured using the intravenous glucose tolerance test).

• In contrast, β-cell function did not improve in the insulin group.

CV implications of insulin resistance and PPARγ activation

- The effects of PPAR modulation on lipids are discussed in the next series of slides.
• In patients with insulin resistance, LDL-C levels are similar to or only slightly elevated compared with the general population. However, it is important to look beyond the numbers to assess global risk in these individuals.

• Patients with insulin resistance have LDL particles that are more atherogenic than the general population because of a shift towards a greater proportion of small, dense particles.

• Small, dense LDL particles arise as follows:
  o Increased FFA flux to the liver stimulates the assembly and secretion of very low-density lipoproteins (VLDL).
  o Elevated VLDL levels promote exchange of cholesterol and triglycerides between VLDL and HDL (an exchange mediated by cholesteryl ester transfer protein).
  o The result is depletion of cholesterol and enrichment of triglycerides in HDL.

• Subsequent hydrolysis of triglycerides within HDL by either lipoprotein lipase or hepatic lipase leads to smaller, denser particles.

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• Small, dense LDL particles have a number of characteristics that make them more atherogenic than normal LDL.\textsuperscript{1} The clinical relevance of these properties is demonstrated in the next slide.

Increased small, dense, LDL particles associated with reduced IHD survival

N = 2072 men without IHD at baseline; 13-year follow-up

1.00
0.90
0.80
Survival probabilities

Follow-up (years)
0 2 4 6 8 10 12

P < 0.001

Tertiles of LDL-C
≤1.07 mmol/l 1.07–1.86 mmol/l 1.86 mmol/l

IHD = ischemic heart disease

• St-Pierre et al followed 2072 subjects for 13 years.¹
• At baseline, all subjects were free from self-reported ischemic heart disease (IHD).
• LDL particles were classified as either large (≥260 Å in diameter) or small (<255 Å in diameter).
• Subjects with a greater proportion of small LDL particles had significantly worse survival.

• Brunzell et al pooled data from three studies of patients with type 2 diabetes and one study of patients with IGT.¹

• All studies evaluated rosiglitazone 8 mg daily, with treatment durations ranging from 8 to 26 weeks.

• Rosiglitazone was associated with significant increases in LDL size and buoyancy.

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Studies suggest that PPARγ activators may have different effects on lipid levels and particle size in patients not receiving concurrent statin therapy.

Goldberg et al reported on a 24-week, randomized, double-blind, parallel-group study in which statin or other lipid-lowering therapy was excluded. In the pioglitazone 45-mg and rosiglitazone 8-mg groups, respectively:

- LDL-C increased by 23% and 16% (P < 0.001).
- HDL-C increased by 15% and 8% (P < 0.001).
- Triglycerides decreased 12% vs increase of 15% (P < 0.001).
- Mean change in LDL diameter was 0.47 nm vs 0.31 nm (P = 0.005).

Plotkin et al conducted a 24-week, randomized, placebo-controlled, parallel-group study of simvastatin 40 mg added to pioglitazone 45 mg or rosiglitazone 8 mg. There were no significant differences between groups in lipid changes, with the exception of triglycerides, where a greater reduction in the rosiglitazone group was observed.

In contrast, Khan et al conducted an open-label study in 305 patients treated with statin plus rosiglitazone; the latter was switched to pioglitazone 30–45 mg for 17 weeks. Decreases in total-C, LDL-C, and triglycerides were noted. There was no change in HDL-C.

Thus, the degree and clinical significance of differences among PPARγ activators with regard to their effects on lipids in patients with diabetes remains controversial.

• The effects of PPAR modulation on obesity-related inflammation are discussed in the next series.
• Adipose tissue is an active organ that secretes several biologically active molecules (adipokines).\textsuperscript{1,2} Most adipokines have pro-inflammatory and atherogenic effects, including C-reactive protein (CRP), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), angiotensinogen, leptin, resistin, and monocyte chemotactic protein-1 (MCP-1).

• Adiponectin is attracting attention, since this adipokine appears to have a number of antiatherogenic effects. Levels of this adipokine are decreased in obesity and correlate inversely with CV risk, as shown on the next slide.

• Using data from the Health Professionals Follow-up Study, Pischon et al conducted a case-control study to assess the relationship between adiponectin and CV risk.¹

• N = 18,225 men were followed for a mean duration of 6 years.

• As shown, subjects with adiponectin levels in the highest quintile demonstrate a significantly lower risk of MI compared with those in the lowest quintile (relative risk, 0.39; 95% CI, 0.23–0.64; P < 0.001).

Adiponectin circulates in serum as either a hexamer of relatively molecular weight or a multimeric structure of high molecular weight (HMW form).\(^1\)

Pajvani et al measured adiponectin levels in a subgroup of 40 participants in the TRIPOD study and found that as insulin sensitivity increased, the proportion of the HMW form also increased (as measured by increasing ratio of HMW-to-total adiponectin).

Investigators have also hypothesized that hyperinsulinemia, secondary to insulin resistance, downregulates adiponectin synthesis by adipocytes, while improved insulin sensitivity with PPAR\(\gamma\) activation upregulates adiponectin synthesis.

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• Circulating IL-6 triggers synthesis of CRP by the liver. In addition, recent studies suggest that adipose tissue may also be a source of CRP. Chronic inflammation and hyperglycemia contribute to development of insulin resistance.¹

• PPARγ activation improves insulin sensitivity by blunting both inflammation and glucotoxicity.

• Ridker et al used data from the Women’s Health Study to assess whether CRP adds prognostic information to the metabolic syndrome.¹

• N= 14,719 women free from diabetes at baseline were followed-up for 8 years. The metabolic syndrome was diagnosed using modified ATP III criteria, replacing waist circumference >35 in with BMI >26.7 kg/m² to define obesity.²

• Incident CV events included nonfatal MI, nonfatal ischemic stroke, coronary revascularization, and CV death.

• Data confirmed previous studies that demonstrate an increased risk for the development of CV disease when metabolic syndrome components are added. Moreover, data show that CRP levels ≥3 mg/L are associated with a further increase in risk.

• These observational data are consistent with experimental data linking inflammation to both insulin resistance and atherosclerosis.

• Festa et al studied the association of new-onset diabetes and inflammatory activity in 1047 individuals free from diabetes at baseline.$^1$

• Over a 5-year follow-up, subjects who developed diabetes had significantly higher baseline levels of CRP and PAI-1 ($P < 0.001$ for upper vs lower quartiles). A similar trend was observed for fibrinogen ($P = 0.06$).

• These findings support the hypothesis that inflammation has an important role in the pathogenesis of both diabetes and atherosclerosis.

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• Haffner et al randomized 357 patients with type 2 diabetes to receive either rosiglitazone 4 mg or 8 mg, or placebo for 26 weeks.¹

• As shown, both doses of the PPARγ activator significantly reduced CRP levels compared with placebo (P < 0.05).

CV implications of insulin resistance and PPARγ activation

- The effects of PPAR modulation on hypertension in the insulin resistance syndrome are discussed in the next series of slides.
Raji et al measured 24-h ambulatory BP and insulin sensitivity in 24 hypertensive patients free from diabetes who received rosiglitazone 8 mg (along with usual antihypertensive medications) for 16 weeks.\(^1\)

Subjects were classified as either “low renin” (n = 12) or “nonmodulators” (n = 12). Previous studies had indicated that nonmodulators were a subgroup of patients with salt-sensitive hypertension who were more insulin resistant than low-renin patients.

In both groups, there was a significant correlation between improvement in insulin sensitivity and modest decline in mean 24-h blood pressure.

The investigators concluded that mechanisms remain to be fully elucidated. Close relationships exist between the changes in insulin sensitivity and blood pressure across hypertension subgroups. Common physiologic mechanisms are most likely responsible.

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• The findings by Raji et al were extended by Home and colleagues in 668 persons with type 2 diabetes and loss of glucose control.¹

• Patients on metformin monotherapy were randomized to rosiglitazone or sulfonylurea. Those with loss of glucose control on sulfonylurea monotherapy were randomized to rosiglitazone or metformin.

• Data show that, regardless of baseline therapy, addition of rosiglitazone resulted in modest but sustained reduction in 24-h ambulatory blood pressure.

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- The effects of PPAR modulation on thrombolytic balance in the insulin resistance syndrome are discussed in the next series of slides.
Hamaguchi et al demonstrated that the inflammatory adipokine tumor necrosis factor-α (TNF-α) promotes secretion of PAI-1 by human umbilical-vein endothelial cells in a dose-dependent manner.\(^1\)

- PPARγ activation with troglitazone blunted this effect.

- Similar effects have also been demonstrated in humans, as the next two slides show.

• Nagi et al randomized 27 persons with type 2 diabetes to metformin 2.5 g or placebo for 12 weeks.¹

• At study end, PAI-1 activity was significantly lower in the metformin group than in the placebo group (difference of 5.3 U/mL, P = 0.001).

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• Weissman et al treated type 2 diabetic subjects with open-label metformin 500 mg bid for at least 3 weeks then randomized the group to receive either rosiglitazone or to continue on metformin.¹

• Weeks 1 through 8 (daily dose) (data not shown):
  o Rosiglitazone 4 mg plus metformin 1000 mg
  o Metformin 1500 mg

• Weeks 8 through 24 (daily dose):
  o Rosiglitazone 8 mg plus metformin 1000 mg
  o Metformin 2000 mg

• As shown, combined insulin sensitizer therapy was associated with significantly greater reductions in CRP and PAI-1. Levels of matrix metalloproteinase-9 (MMP-9) rose in the metformin group and decreased in the thiazolidinedione group.

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• This section summarizes provocative new data that suggests PPARγ activation may be associated with reduction in CV events as well as the ongoing clinical studies that are testing this hypothesis.
• Endothelial function is impaired early in insulin resistance.

• Mather et al randomized 44 patients with type 2 diabetes to metformin 1 g or placebo for 12 weeks.¹

• Before and after treatment, endothelium-dependent and endothelium-independent vasodilation was assessed by intra-arterial administration of acetycholine or sodium nitroprusside, respectively.

• As shown, metformin was associated with a significant improvement in endothelium-dependent vasodilation compared with placebo.

• This finding supports a link between insulin resistance and endothelial dysfunction.

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• Pistroch et al conducted 12-week double-blind crossover trial in 19 patients with type 2 diabetes.¹

• Subjects with microalbuminuria remained on their baseline oral hypoglycemic drug and were crossed over from placebo to rosiglitazone. Those without microalbuminuria were crossed over from nateglinide to rosiglitazone.

• In both groups, rosiglitazone was associated with improvements in GFR and reduction in proteinuria.

• Quiñones et al treated 16 insulin-resistant patients with rosiglitazone 8 mg for 3 months. Endothelial function improved with treatment, as shown by increased coronary vasodilation in response to the cold pressor test.1

• Following cessation of treatment, endothelial function declined.

Accumulated data indicate that reduction in carotid atherosclerosis is common to all thiazolidinediones.¹

Minamikawa et al randomized 135 patients with type 2 diabetes to troglitazone 400 mg plus usual care (sulfonylureas or diet) or usual care alone for 6 months.¹

Koshiyama et al randomized 106 patients with type 2 diabetes to pioglitazone 30 mg plus usual care (sulfonylureas or diet) or usual care alone for 6 months.²

Sidhu et al randomized 92 patients with stable CAD but no diabetes to rosiglitazone or placebo for 12 months.³

Langenfeld et al randomized 173 patients with type 2 diabetes to pioglitazone 45 mg or glimepiride 1 to 6 mg (average of 2.7 mg) for 6 months.⁴

• Sidhu et al randomized 92 consecutive nondiabetic subjects with stable CAD to placebo or rosiglitazone 4 mg once daily for 8 weeks, followed by 8 mg daily for 40 weeks. The data on the slide are from the 80 subjects who completed the study.

• The PPARγ-activator group showed reduced progression of carotid intima-media thickness (IMT) compared with the placebo group (decrease of 0.012 mm vs increase of 0.031 mm, respectively, P = 0.03).

• A study by Langenfeld et al provided further insight into the antiatherosclerotic effect of PPARγ activation.¹

• N = 173 adults with type 2 diabetes were randomized to pioglitazone 45 mg or glimepiride 2.7 mg for 24 weeks. Carotid IMT was measured via B-mode ultrasound.

• Both treatments were associated with similar glucose control: A1C decreased from 7.52% to 6.72% in the PPARγ-activator group and from 7.44% to 6.84% in the sulfonylurea group (P = 0.1291 for between-group comparison).

• Carotid IMT was significantly reduced from baseline in the PPARγ-activator group (0.033 mm; P < 0.005), but not in the sulfonylurea group (0.002 mm reduction) (P < 0.001, between-group comparison).

• Thus, the effect of PPARγ activation on atherosclerotic progression is independent of glucose lowering.

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• Studies have convincingly demonstrated the reduction of atherosclerosis progression with statins. Since statins and PPARγ activation blunt disease progression via different mechanisms, it is logical to expect that their effects would be additive. Corti et al tested this hypothesis in rabbits.

• Aortic atherosclerosis was induced by a high-cholesterol diet in conjunction with injury to the vessel wall. The animals were randomized to either continue a high-cholesterol diet, a normal diet, or normal diet augmented with the statin simvastatin with and without the experimental PPARγ activator L-805645. The investigators used vessel wall area (visualized by magnetic resonance imaging [MRI]) as a measure of atherosclerosis progression.

• A significant progression in vessel wall area of 15% was observed in the high-cholesterol–diet group (P < 0.01).

• Progression was blunted or reversed in the other groups:
  - Normal diet, 2.5% reduction
  - PPARγ activator, 4.5% reduction
  - Statin, 12% reduction
  - PPARγ activator plus statin, 22% reduction (P = 0.03 vs PPARγ activator alone and P = 0.04 vs statin alone)

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- Wang et al induced neointimal hyperplasia in mice via femoral angioplasty. The animals also received either rosiglitazone 8 mg/kg or saline for 2 weeks prior to and 4 weeks after angioplasty. The investigators used the ratio of intimal area to medial area (I/M ratio) as a measure of neointimal proliferation.

- The I/M ratio was 3.1 in controls and 0.98 in the PPARγ-activator group (P < 0.001). The arrows in the cross-sectional images above the graph indicate the vascular medial layer.

- The antiproliferative effects of PPARγ activation have also been demonstrated in humans, as the next slide demonstrates.

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Accumulated data in human studies confirm that thiazolidinediones blunt neointimal proliferation in patients with type 2 diabetes who undergo stenting.

A series of three reports from a Japanese group evaluated troglitazone added to diet or conventional glucose-lowering therapy, or pioglitazone added to conventional glucose-lowering therapy.\(^1\)\(^-\)\(^3\)

A fourth, smaller, trial found a trend toward benefit with rosiglitazone added to metformin or other glucose-lowering therapy. However, in this trial the thiazolidinedione was added after stenting (in contrast with the other trials, which added the drug prior to stenting). In addition, a low dose of rosiglitazone (4 mg) was given in the first month, with a full dose (8 mg) given for the remainder of the trial.\(^4\)

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• One day prior to scheduled percutaneous coronary intervention (PCI), Choi et al randomized 95 patients with type 2 diabetes to one of two groups:1:
  o Rosiglitazone 8 mg prior to catheterization, and 4 mg daily thereafter, added to baseline antidiabetic therapy.
  o Baseline antidiabetic therapy only (control group).
• All subjects underwent stent implantation during the procedure.
• As shown, at 6 months there was a significantly lower rate of in-stent restenosis in the PPARγ-activator group (data shown: n = 83 evaluable patients).

• Koro et al used a case-control study design to examine the relation between antidiabetic treatment and MI in patients with type 2 diabetes between 1997 and 2002.¹

• Patients with type 2 diabetes and first MI (n = 229) were identified through the Integrated Healthcare Information Services managed care database. These cases were matched with subjects (controls) with incident MI but no diabetes (n = 1374).

• Compared with insulin monotherapy, oral agents reduced risk of CV events. Greatest relative risk reduction (49%) was observed with thiazolidinedione treatment.

• Masoudi et al reported a retrospective cohort study of 16,417 Medicare beneficiaries with diabetes who were discharged with a principal diagnosis of heart failure.¹

• As shown, mortality among those receiving thiazolidinedione therapy (mean age 75.9 years, n = 2226) was lower than in those not receiving thiazolidinedione therapy (mean age 77 years, n = 12,069). The adjusted hazard ratio (HR) was 0.87 (95% CI, 0.88–0.94).

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• Another class of insulin sensitizer, metformin, was associated with a 14% relative risk reduction in mortality (HR, 0.86; 95% CI, 0.78–0.97; data not shown).¹

Neutral effect of PPARγ activation and metformin on hospital readmission

N = 16,417 with diabetes and HF

<table>
<thead>
<tr>
<th>Hospital readmission</th>
<th>All-cause</th>
<th>HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>TZD</td>
<td>1.04 (0.99–1.10)</td>
<td>1.06 (1.00–1.12)</td>
</tr>
<tr>
<td>Metformin</td>
<td>0.94 (0.89–1.01)</td>
<td>0.92 (0.86–0.99)</td>
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• There were no differences in the risk for all-cause readmission among patients discharged on a thiazolidinedione or metformin Rx compared with those not receiving either drug.
• There was a modestly higher risk (of borderline significance) for heart failure readmission with a thiazolidinedione Rx and a significantly lower risk with a metformin Rx.
• The investigators concluded, “This observational study suggests that thiazolidinediones and metformin are not associated with increased mortality and may improve outcomes in older patients with diabetes and heart failure.”
• Because of the potential for fluid retention with thiazolidinedione therapy, in 2003 the AHA and ADA jointly issued a consensus statement advising caution with these agents in patients with diabetes and coexisting heart failure.¹

• The AHA/ADA recommendations are summarized on the slide.

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Inzucchi et al conducted a retrospective cohort study of 8872 Medicare beneficiaries with diabetes. Subjects were discharged after hospitalization with MI between April 1998 and March 1999 or July 2000 to June 2001; 819 with a thiazolidinedione Rx, 1273 metformin Rx, and 139 receiving both drugs.

Metformin or thiazolidinediones had a neutral effect on mortality compared with treatment that did not include an insulin sensitizer:
- Metformin: Hazard ratio (HR) 0.92 (0.81–1.06)
- Thiazolidinediones: HR 0.92 (0.80–1.05)

Mortality risk was nearly 50% lower in patients receiving both drugs:
- Metformin + thiazolidinediones: HR 0.52 (0.34–0.82).

Patients prescribed thiazolidinediones (alone or in combination with metformin) had a higher risk of readmission for heart failure probably due to drug-related peripheral edema.¹

Increases in heart failure readmissions were not associated with increased mortality.

• The United Kingdom Prospective Diabetes Study (UKPDS) randomized patients with newly diagnosed type 2 diabetes to metformin (n = 342; target fasting glucose of 108 mg/dL), other hypoglycemic medication (either chlorpropamide, glibenclamide, or insulin) (n = 951; target fasting glucose of 108 mg/dL), or usual care (n = 411). The median duration was 10.7 years.

• Relative to usual care, metformin was associated with a 36% relative risk reduction in all-cause mortality (RR, 0.64, 95% CI, 0.45–0.91). The other intensive treatments combined were associated with an 8% relative risk reduction (RR, 0.92; 95% CI, 0.71–1.18) (P = 0.021, comparison between the two intensive-treatment groups).

• There was no difference between the two intensive-treatment groups in the relative risk reductions in stroke and MI, although the trend was in favor of metformin.

• These data suggest that insulin-sensitizing therapy may be associated with greater reductions in CV outcomes than other hypoglycemic therapies.

Data from surrogate outcomes studies and large observational studies suggest that thiazolidinediones may reduce CV outcomes in patients with insulin resistance or frank diabetes. Clinical outcomes studies to test this hypothesis are underway.
A number of large, multicenter trials are assessing the effects of PPARγ activation on complications of type 2 diabetes (DM) and insulin resistance syndrome.

**Anticipated in 2007:**
- **ADOPT**\(^1\): N ≥600; drug-naïve patients with type 2 diabetes of ≤3 years duration. The trial compares the duration of glucose control achieved by monotherapy with rosiglitazone 8 mg, metformin 2 g, or glyburide 15 mg.
- **APPROACH**\(^2\): N ≥34; DM and CV disease; compares effects of rosiglitazone and glipizide on progression of atherosclerosis (measured by IVUS).
- **CHICAGO**\(^3\): DM and asymptomatic CAD; compares effects of TZD therapy (pioglitazone) and sulfonylurea (glimepiride) on carotid IMT.

**Anticipated in 2008:**
- **ACT-NOW**\(^4\): N ≥600; IGT and ≥1 components of insulin resistance syndrome. Primary outcome: new-onset DM.
- **NAVIGATOR**\(^3,5\): N ≥9150; IGT and prior CV disease or with CVD risk factors randomized (2×2 factorial design) to insulin secretagogue nateglinide, valsartan, their combination, or placebo. Primary outcomes: CV events and new-onset DM.
- **PERISCOPE**\(^3\): DM and symptomatic CAD requiring angiography (same randomization as CHICAGO). Primary outcome: percent change from baseline in atheroma volume (measured by IVUS).
- **RECORD**\(^3\): N ≥4000; DM; assesses effects of rosiglitazone on fatal and nonfatal CV events and on glucose control when added to conventional glycemic control with metformin plus sulfonylurea.
- **VADT**\(^4\): N ≤700; DM; compares effects of intensive and less intensive glucose control on fatal/nonfatal CV events.

**Anticipated in 2009:**
- **ACCORD**\(^3,4\): N ≥10,000; DM at high risk for CV events (2×2 factorial design); compares effects of 1) intensive vs less intensive glucose control and 2) intensive vs less intensive BP and lipid control on fatal/nonfatal CV events.
- **BARI-2D**\(^6\): N ≥2800; DM and stable CAD (2×2 factorial design); compares effects of both 1) revascularization/medical therapy vs medical therapy and 2) insulin-sensitizing treatment of DM (rosiglitazone and metformin) vs insulin-providing treatment (sulfonylurea and insulin), both achieving a similar goal of glycemic control, on fatal/nonfatal CV events.
- **ORIGIN**\(^4\): N ≥10,000; ≥1 CV risk factors plus IFG or IGT, or with recent DM (2×2 factorial design); assesses effects of insulin glargin, omega-3-fatty acids, or standard glycemic control on CV events.

5. The NAVIGATOR Trial Steering Committee. NAVIGATOR trial screening suggests that abnormal glucose tolerance is common in people at risk for cardiovascular disease (CVD). *Diabetes.* 2003;52(suppl 1):A505. Abstract 2187-PO.
### PROactive: Study design

<table>
<thead>
<tr>
<th>Objective</th>
<th>Assess the effects of pioglitazone on reducing macrovascular events in type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Randomized double-blind, controlled outcome</td>
</tr>
<tr>
<td>Population</td>
<td>N = 5238 with type 2 diabetes and history of macrovascular disease</td>
</tr>
<tr>
<td>Treatment</td>
<td>Pioglitazone (up to 45 mg) or placebo</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Composite of all-cause mortality, MI, ACS, coronary or peripheral revascularization, amputation, stroke</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Individual components of primary outcome, CV mortality</td>
</tr>
<tr>
<td>Follow-up</td>
<td>4 years</td>
</tr>
</tbody>
</table>

- PROactive was conducted in 5238 patients with type 2 diabetes and at high risk of CV events due to atherosclerotic disease of the coronary, cerebral, or peripheral arteries.\(^1,2\)
- Subjects were randomized to pioglitazone (initial dose 15 mg, with forced titration to 30 mg or 45 mg, depending on tolerability) or placebo.

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The high-risk status of study subjects is demonstrated by the high prevalence of concomitant CV morbidity.¹

---

• At baseline, study subjects were taking a number of drugs known to reduce CV risk.¹

• The primary outcome (all-cause mortality, nonfatal MI, stroke, acute coronary syndromes, leg amputation, coronary or peripheral revascularization) was reduced a nonsignificant 10% over 36 months in pioglitazone patients (compared with placebo).

• However, confirmed divergence in the survival curves suggests that significant risk reduction might have been achieved with longer treatment duration.

---

• The main secondary outcome of all-cause mortality, MI, or stroke was significantly reduced 16% in pioglitazone patients compared with placebo.¹

**PROactive: Summary**

Pioglitazone added to standard antidiabetic and CV therapies showed:

- **10% RRR in primary outcome**
  - Composite all-cause mortality, nonfatal MI (including silent MI), stroke, ACS, leg amputation, coronary or leg revascularization
- **16% RRR in secondary outcome**
  - All-cause mortality, nonfatal MI (excluding silent MI) or stroke
- No difference between groups in HF mortality
- Continued divergence in survival curves
  - Greater benefit with longer treatment duration hypothesized

PROactive results support use of PPARγ modulator in patients with diabetes at high CVD risk
  - May improve CVD outcomes and need to add insulin

- Overall findings of PROactive were positive,¹ but more studies are needed.
- In an accompanying editorial, Yki-Järvinen concluded, “[PROactive] showed that pioglitazone is beneficial in patients with type 2 diabetes and pre-existing macrovascular disease who do not develop heart failure.”²
- Studies are needed to:
  - Confirm the benefit of thiazolidinediones in patients with type 2 diabetes
  - More fully characterize the mechanism of benefit
  - More fully characterize the mechanism and prognosis of treatment-related heart failure

---

The Diabetes Reduction Approaches with Ramipril and Rosiglitazone Medication (DREAM) is being conducted in 5269 patients with IGT or IFG.¹

The trial uses a 2×2 factorial design to compare rosiglitazone 8 mg vs placebo, and ramipril 15 mg vs placebo.

Primary outcomes are new-onset diabetes and all-cause mortality.

Secondary outcomes:

- A composite of CV events (MI, stroke, CV death, coronary revascularization, heart failure, angina, and ventricular arrhythmia requiring resuscitation) and renal events (progression of normoalbuminuria to microalbuminuria or macroalbuminuria, or of microalbuminuria to macroalbuminuria, or a 30% decrease in creatinine clearance).

The STARR substudy (n = 1427) will assess effects of the treatment of carotid atherosclerosis as measured by B-mode ultrasound.

Results are anticipated in 2006.

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The DREAM population is at high risk of diabetes, as shown by the high prevalence of components of the insulin resistance syndrome.¹

---

A Diabetes Outcome Progression Trial (ADOPT) is a multicenter international study designed to test the hypothesis that improving insulin sensitivity in drug-naïve patients with type 2 diabetes may alter disease progression.1

Subjects are randomized to a treatment period of up to 4 years with rosiglitazone ≤8 mg, metformin ≤2 g, or glyburide ≤15 mg. Uptitratio of study medication is required for fasting plasma glucose ≥140 mg/dL.

The primary outcome is the point at which patients attain a fasting plasma glucose ≥180 mg/dL despite maximal monotherapy.

The study also assesses treatment effects on β-cell function and CV risk factors.

Identifying and Treating Patients with Insulin Resistance
• Impaired fasting glucose (IFG) and IGT (measured following consumption of the equivalent of 75 g anhydrous glucose) are recognized markers of a prediabetic state.

• As shown, the American Diabetes Association (ADA) and a task force created by the American Association of Endocrinologists (AACE) and the American College of Endocrinology (ACE) differ slightly in their definitions.¹ ²

• However, there is consensus regarding glucose levels that are diagnostic for diabetes.¹ ²

• IFG is most commonly used in the diagnosis of the insulin resistance syndrome (in conjunction with other clinical parameters as discussed in the following slides).

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### Metabolic syndrome diagnosis:
**ATP III emphasizes clinical practice**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Defining level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity (in)</td>
<td>Waist:</td>
</tr>
<tr>
<td>Men</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;35</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>≥150</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;50</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>≥130/≥85</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>≥110 (ADA ≥100)</td>
</tr>
</tbody>
</table>

- ATP III bases the diagnosis of the metabolic syndrome on the presence of ≥3 of the following easily measured parameters¹,²:
  - Abdominal obesity (assessed by waist circumference, measured midway between the bottom of the rib cage and the iliac crest)
  - Elevated triglycerides
  - Low HDL-C
  - Elevated blood pressure
  - High fasting glucose

- The ICD-9 code for the metabolic syndrome (as defined by these criteria) is 277.7, although Medicare allows physicians to use other codes as appropriate.

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The International Diabetes Federation (IDF) definition of metabolic syndrome is similar to that of the ATP III report, but with a greater focus on central obesity.\(^1\)

Waist circumference is measured midway between the bottom of the rib cage and the iliac crest.\(^2\)

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• The IDF also avoids a “one size fits all” approach to defining central obesity.\(^1\)
• As shown, different cutpoints are used depending on an individual’s gender or ethnicity.

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Metabolic syndrome diagnosis: WHO emphasizes central role of insulin resistance

**Insulin resistance**
- Type 2 diabetes, or
- Impaired fasting glucose, or
- If fasting glucose <110 mg/dL, glucose uptake below lowest quartile

**Plus any 2 of the following:**
- Antihypertensive medication and/or BP ≥140/90 mm Hg
- Plasma triglycerides ≥150 mg/dL
- HDL-C <35 mg/dL (men) or <39 mg/dL (women)
- BMI >30 kg/m² and/or waist-hip ratio >0.9 (men); >0.85 (women)
- Urinary albumin excretion rate ≥20 µg/min or albumin-creatinine ratio ≥30 mg/g


• ATP III requires explicit demonstration of insulin resistance for the diagnosis of the metabolic syndrome. In contrast, the criteria suggested by a consultation group of the World Health Organization (WHO) make insulin resistance a required component for diagnosis, in recognition of the central role it plays in the pathophysiology of the metabolic syndrome.¹ ²

• Insulin resistance is defined as one of the following:
  - Type 2 diabetes
  - Impaired fasting glucose
  - Impaired glucose tolerance
  - Glucose uptake below the lowest quartile for background population under hyperinsulinemic, euglycemic conditions (fasting glucose <110 mg/dL).

• Two additional risk factors are required for a diagnosis of the metabolic syndrome.

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Other markers of insulin resistance

- Family history of type 2 diabetes or CAD
- Overactive sympathetic nervous system
- ↑ Uric acid

- Simple criteria help identify insulin-resistant patients.
- The ATP III criteria for diagnosing metabolic syndrome may not identify all patients with insulin resistance.
- Cohn et al\(^1\) reviewed relevant studies to identify additional, easily measured criteria that might aid in diagnosis.

---

• Compelling evidence from randomized clinical trials supports the use of four classes of therapies for CV risk reduction that can be remembered by a simple mnemonic, ABC:\textsuperscript{1}:
  \begin{itemize}
    \item A: ACE inhibitors
      \begin{itemize}
        \item Antiplatelet agents (aspirin)
      \end{itemize}
    \item B: Beta-blockers
      \begin{itemize}
        \item BP control
      \end{itemize}
    \item C: Cholesterol management
  \end{itemize}
• Important lifestyle recommendations can be incorporated into the mnemonic:
  \begin{itemize}
    \item D: Diet
      \begin{itemize}
        \item Don’t smoke
      \end{itemize}
    \item E: Exercise
  \end{itemize}

\textsuperscript{1} Cohen JD. ABCs of secondary prevention of CHD: Easier said than done. \textit{Lancet}. 2001;357:972-973.
• This slide summarizes the findings of a conference cosponsored by the American Heart Association (AHA) in partnership with the National Heart, Lung, and Blood Institute (NHLBI), and by the ADA, devoted to clinical management of the metabolic syndrome.

• Conference findings1:
  ○ Risk assessment using the Framingham Risk Score was recognized to be critical for setting goals of therapy.
  ○ Given the increasing evidence that suggests a role for inflammatory processes in the metabolic syndrome, conference participants also recognized that C-reactive protein (CRP) testing may also be carried out at the physician’s discretion.
  ○ Drug therapy may be necessary in many patients to achieve recommended goals. Specifically, medical therapy would be used to help in control of lipids, blood pressure, glucose, and to reduce risk of thrombosis.

• The emerging role of improving insulin sensitivity was also noted. Pharmacotherapies that improve insulin sensitivity have the potential to improve insulin resistance.

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• Incidence of type 2 diabetes (average follow-up, 2.8 years): 11 cases/100 person-years in the placebo group vs 7.8 in the metformin and 4.8 in the lifestyle-intervention groups (data not shown).\textsuperscript{1}
  o This represents a reduction of 58% in diabetes incidence with lifestyle interventions and 31% with metformin.

• The effects were similar in both men and women and in all racial and ethnic groups. Intensive lifestyle intervention was at least as effective in older as in younger participants.

• Results support the hypothesis that type 2 diabetes can be prevented or delayed in persons who are at high risk for the disease by treatment with metformin and lifestyle modification.
  o Lifestyle intervention was particularly effective—1 case of diabetes was prevented per 7 persons treated for 3 years.

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The slide compares the effect of tight control of both BP and glycemia on a number of outcomes in patients with type 2 diabetes in the UK Prospective Diabetes Study (UKPDS).¹

Over 10 years, hemoglobin A₁c (A1C) was 7.0% in the intensive group vs 7.9% in the conventional group, an 11% reduction, and associated with a reduced risk in some outcomes.

Tight blood-glucose control reduced the risk for any diabetes-related endpoint by 12% (P = 0.029). There was a significant 25% risk reduction (P = 0.0099) in microvascular endpoints, including the need for retinal photocoagulation and a nonsignificant risk reduction of 10% for any diabetes-related death (P = 0.34) and 6% for all-cause mortality (P = 0.44).

Thus, intensive blood-glucose control substantially decreases the risk of microvascular complications in patients with type 2 diabetes, but it does not reduce risk of macrovascular disease.

By comparison, patients in the tight BP-control group achieved a mean BP of 144/82 mm Hg vs 154/87 mm Hg with less-tight control.¹ Tight BP-control was associated with significant reductions for any diabetes-related outcome (24%, P = 0.0046), deaths related to diabetes (32%, P = 0.019), microvascular disease (37%, P = 0.0092), stroke (44%, P = 0.013), and heart failure (56%, P = 0.0043).

As seen here, more substantial risk reductions in diabetes complications were achieved with tight BP control.

¹ UK Prospective Diabetes Study (UKPDS) Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. BMJ. 1998;317:703-713.
Two recent large trials provide compelling evidence for the importance of LDL-C lowering in persons with diabetes.

**HPS**: The Heart Protection Study included 5963 persons with diabetes (33% prior CHD) randomized to simvastatin 40 mg daily or placebo regardless of baseline lipid levels. Primary outcome: MI or coronary death; mean follow-up, 4.8 years.

**Results:**
- LDL-C: Statin treatment reduced LDL-C from 124 mg/dL to 85 mg/dL.
- Primary outcome: 27% relative risk reduction (RRR) in MI or coronary death and 24% RRR in stroke (P < 0.0001, both comparisons).
- Patients with diabetes but without CHD or other vascular disease at baseline: 33% RRR—similar to reduction achieved in the group without diabetes (27% primary outcome).

**CARDS**: The Collaborative AtoRvastatin Diabetes Study was the first prospective evaluation of a statin in a population comprised solely of persons with type 2 diabetes. CARDS randomized 2838 patients with type 2 diabetes plus ≥1 other CV risk factors (but no history of CHD, MI, or stroke) to atorvastatin 10 mg or placebo. Primary outcome: composite of major coronary events, revascularization, unstable angina, resuscitated cardiac arrest, and stroke. Study was terminated 2 years early, after median follow-up of 3.9 years.

**Results:**
- LDL-C: Statin treatment reduced LDL-C from 118 mg/dL to 82 mg/dL.
- Primary outcome: 37% RRR (HR, 0.63; 95% CI 0.48–0.83; P = 0.001); 48% RRR (HR, 0.52; 95% CI, 0.31–0.89; P value not reported).

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• In the BP-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), atorvastatin 10 mg showed significant improvement in cardiovascular parameters in patients with diabetes and hypertension.¹

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• In MICRO-HOPE, Kaplan Meier curves show an early and consistent benefit of ramipril 10 mg in patients with diabetes. There was a 25% relative risk reduction in the primary outcome of MI, stroke, or CV death ($P = 0.0004$).  

• In PERSUADE, treatment with perindopril 8 mg once daily for 5 years reduced the primary outcome of CV death, MI, and cardiac arrest by 19% ($P = 0.131$).

• The results of PERSUADE support and extend the observations in MICRO-HOPE to a somewhat lower-risk population of diabetic patients.

In Steno-2, patients in the conventional-therapy group received usual care according to the 1998 and 2000 recommendations of the Danish Medical Association.

The intensified-intervention group received the following:

- ACEI or ARB ± diuretic/CCB/β-blocker
- Metformin or gliclazide
- Atorvastatin
- Fibrate
- Aspirin and vitamin supplementation

• Multifactorial intervention reduced CV outcomes.

• Significantly more patients in the intensive-treatment group reached goals.

• There was a 53% reduction in the primary outcome, a composite of death from CV causes, nonfatal MI, nonfatal stroke, revascularization, and amputation.¹

• The continued divergence in rates of primary outcome suggests that therapy for even longer periods might achieve an even better prognosis.

Insulin resistance, as clinically manifest in the metabolic syndrome, is highly prevalent in the patient population commonly seen by cardiologists.

Although individual risk factors of the metabolic syndrome may not be substantially greater than the general population, the synergistic interaction of these risk factors (driven in large part by insulin resistance) places these patients at high global risk for CV events.

Activation of PPARγ receptors with thiazolidinediones has broad ranging effects on insulin sensitivity, inflammation, and atherosclerosis progression.

A number of outcomes studies are in progress to more fully characterize the therapeutic potential of this approach.