# Cardiovascular Impact of Diabetic Agents

**ACCORD, ADVANCE, VADT, UKPDS 10yr, PERISCOPE, PROactive**

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**Edited By:** Richard J. Kraft, Pharm.D.

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## Highlights: The Quick-Read Information  
(Answers)

1. Cardiovascular events are responsible for two thirds of deaths in patients with Type 2 Diabetes Mellitus  
   a. True  
   b. False
2. Which class of Diabetic agents is contraindicated in NYHA Class III or IV?  
   a. Meglitinides  
   b. Sulfonylureas  
   c. Thiazolidinediones  
   d. DPP4 inhibitors
3. Which diabetic medication(s) should be avoided in T2DM patients with known CAD?  
   a. 1st generation sulfonylureas  
   b. pioglitazone  
   c. metformin/repaglinide
4. Meglitinides can be thought of as “short-acting sulfonylureas” and are given at meal times.  
   a. True  
   b. False
5. Metformin is an appropriate treatment choice in overweight T2DM patients.  
   a. True  
   b. False
6. The FDA has removed Avandia from the market due to its heart failure potential.  
   a. True  
   b. False

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**Drug Classes in Review:**

- Sulfonylureas  
- Biguanides  
- Alpha-Glucosidase Inhibitors  
- Thiazolidinediones  
- Meglitinides  
- Incretin Mimetics  
- DPP4 Inhibitors  
- Amylin Analogs  
- Insulin
Introduction

Diabetic complications include microvascular, macrovascular, and neuropathic disorders. Cardiovascular events are responsible for two thirds of deaths in patients with Type 2 Diabetes Mellitus. Cardiovascular events have been reported and associated with many of the treatment options for Type 2 Diabetes Mellitus. However, many of the same agents noted to have adverse effects on cardiovascular outcomes have been found to also exhibit advantages on cardiovascular outcomes in different trials.

- The following review summarizes literature evidence of the cardiovascular impact of diabetic agents followed by an interpretation of the results.

Background

Diabetes Mellitus (DM) is a metabolic disorder characterized by insufficient insulin secretion, insulin resistance, or both. Type 1 DM results from the autoimmune destruction of the beta cells of the pancreas. It usually occurs in children and adolescents but can occur at any age. Type 2 DM is characterized by insulin resistance and progressively lower insulin secretion over time.

The primary goals of DM treatment include prevention of microvascular and macrovascular complications, reduce symptoms, and increase quality of life. Insulin treatment is implemented in Type 1 DM and Type 2 DM. Agents used solely in the treatment of Type 2 DM include Sulfonylureas, Biguanides, Alpha-Glucosidase Inhibitors, Thiazolidinediones, Meglitinides, Incretin Mimetics, DPP4- Inhibitors, and Amylin Analogs.

There is conflicting evidence over whether diabetic agents potentiate cardiovascular disease in certain patient types or whether intensive glucose control prevents microvascular and macrovascular diabetic complications. Outweighing the risks versus benefits is something practitioners must do when prescribing oral anti-diabetic agents.

Diabetic Agent Comparative Chart

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drugs within Class -Representatives-</th>
<th>FDA Indications</th>
<th>Non FDA /Off Label Use</th>
<th>Available In Combination</th>
<th>Adverse Effects</th>
<th>IHA Tier</th>
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<tr>
<td>Sulfonylureas</td>
<td>Glyburide (Diabeta) glipizide (Glucotrol, Glucotrol XL) glimepiride (Amaryl)</td>
<td>T2DM</td>
<td>Gestational diabetes</td>
<td>Glyburide/metformin Glipizide/metformin Glimepiride/pioglitazone Glimepiride/rosiglitazone</td>
<td>Hypoglycemia, abdominal pain, diarrhea, dyspepsia, n/v</td>
<td>1</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Metformin (Glucophage)</td>
<td>T2DM</td>
<td>Infertility, polycystic ovarian syndrome, precocious puberty</td>
<td>Glyburide/metformin Glipizide/metformin Metformin/pioglitazone Metformin/rosiglitazone Metformin/repaglinide Metformin/sitagliptin</td>
<td>Anorexia, n/v, abdominal discomfort, dyspepsia, flatulence, diarrhea, dysgeusia</td>
<td>1</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>Acarbose (Precose, Miglitol (Glyset)</td>
<td>T2DM</td>
<td>T1DM</td>
<td></td>
<td>Flatulence, abdominal pain, diarrhea</td>
<td>1</td>
</tr>
<tr>
<td>Thiazolidined-</td>
<td>Rosiglitazone</td>
<td>T2DM</td>
<td>T2DM</td>
<td>Glimepiride/pioglitazone</td>
<td>Back pain,</td>
<td>2</td>
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<td><strong>Glucose Lowering Agents</strong></td>
<td><strong>Examples</strong></td>
<td><strong>Psychiatric Symptoms</strong></td>
<td><strong>T2DM</strong></td>
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<tr>
<td>Meglitinides</td>
<td>Repaglinide (Prandin)</td>
<td>Metformin/repaglinide</td>
<td>Hypoglycemia, Ischemia, Chest pain</td>
<td>T2DM</td>
<td>2</td>
<td></td>
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<tr>
<td></td>
<td>Nateglinide (Starlix)</td>
<td>Metformin/repaglinide</td>
<td></td>
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<td>Incretin Mimetics</td>
<td>Exenatide (Byetta)</td>
<td>Metformin/sitagliptin</td>
<td>Nasopharyngitis, URI, headache</td>
<td>T2DM</td>
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<td></td>
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<tr>
<td></td>
<td>Liraglutide (Victoza)</td>
<td></td>
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<tr>
<td>DPP4 Inhibitors</td>
<td>Sitagliptin (Januvia)</td>
<td>Metformin/sitagliptin</td>
<td>Nasopharyngitis, URI, headache</td>
<td>T2DM</td>
<td>2</td>
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<tr>
<td></td>
<td>Saxagliptin (Onglyza)</td>
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<tr>
<td>Amylin Analog</td>
<td>Pramlintide (Symlin)</td>
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<tr>
<td>Insulin (Rapid Acting)</td>
<td>Aspart (Novolog), glulisine(Apidra), lispro (Humalog)</td>
<td>Diabetic ketoacidosis</td>
<td>Novolog mix 70/30 Humalog 50/50 Humalog 75/25</td>
<td>T1DM T2DM</td>
<td>2</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Hypoglycemia, weight gain</td>
<td>3</td>
<td></td>
<td></td>
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<tr>
<td>Insulin (Regular)</td>
<td>Novolin R</td>
<td>Regular/NPH</td>
<td>Hypoglycemia, weight gain</td>
<td>T1DM T2DM</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Insulin (Intermediate)</td>
<td>NPH</td>
<td>Regular/NPH</td>
<td>Hypoglycemia, weight gain</td>
<td>T1DM T2DM</td>
<td>2</td>
<td></td>
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<tr>
<td>Insulin (Long Acting)</td>
<td>Glargine (Lantus)</td>
<td>Regular/NPH</td>
<td>Hypoglycemia, weight gain</td>
<td>T1DM T2DM</td>
<td>2</td>
<td></td>
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<tr>
<td></td>
<td>Detemir (Levemir)</td>
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</table>

- **Diabetes Type 1 (T1DM)**
- **Diabetes Type 2 (T2DM)**
- **Insulin**: Novolog, Apidra, Humalog, Lantus, Levemir
- **Side Effects**: Hypoglycemia, weight gain, headache, nausea/vomiting, diarrhea, fatigue, edema, injury, URI, sinusitis, acid reflux, anorexia, chest pain, chest discomfort, coughing, dizziness, fatigue, pharyngitis, arthralgia.
Literature Review

1. Sulfonylureas and Insulin

**UKPDS**:  

**Background**: UK Prospective Diabetes Study was designed to assess whether intensive blood-glucose control reduced the risk of macrovascular or microvascular complications and which therapy was most advantageous. A previous study (UGDP, 1971) found evidence that the sulfonylurea, tolbutamide, increased the risk of cardiovascular mortality. A new hypothesis was formed: increased myocardial damage from inhibition of ATP-K\(^+\) channel opening in patients with myocardial ischemia due to sulfonylurea binding to the cardiovascular SUR2 receptor. This could also induce a ventricular arrhythmia. Exogenous insulin has also been linked to cardiovascular adverse effects because in vitro studies with raised insulin concentrations induced atheroma and myocardial infarction. Therefore, this study tested the risk of cardiovascular complications of sulfonylurea OR insulin therapy compared to diet treatment only.

**Methods**: 3867 newly diagnosed Type 2 DM Patients were randomly assigned intensive treatment with a sulfonylurea (chlorpropamide, glibenclamide, or glipizide), insulin, or conventional treatment with diet. Goal of FBG was less than 6 mmol/L (~108 mg/dL) in the intensive group and best achievable FBG for the conventional diet group.

**Results**: Median follow up for endpoint analysis was 10 years; at this time, an 11% decrease in median A1c was noted in the intensively treated groups. No difference was found in the rate of myocardial infarction or diabetes-related death between the sulfonylurea and insulin groups. [Note: These two drugs essentially do the same thing, thus difference here would actually be surprising]. An increase in myocardial infarction in patients assigned insulin was not found. There was no evidence of harmful cardiovascular effects of sulfonylureas or insulin therapy.

**Conclusion**: The UKPDS data does not support the hypothesis of the UGDP study that sulfonylureas exhibit adverse cardiovascular effects or that insulin treatment induces atheroma and MI. UKPDS shows that an intensive glucose-control treatment maintains an 11% lower A1c, and do not effect macrovascular complications. [Note: Patients from the insulin or sulfonylurea group may have been given metformin in the post-trial period, potentially skewing the results of observed benefits.]

- The benefits of intensive treatment outweigh the potential risks.

2. Biguanides (Metformin)

**Holman et al.**: Re:UKPDS 10-yr Follow Up

**Background**: Post-trial monitoring of the United Kingdom Prospective Diabetes Study (UKPDS) was done to determine whether improved glucose control with metformin had a long-term effect on macrovascular outcomes.

**Methods**: UKPDS trial as explained in previous study mentioned above, but patients more than 120% of their ideal body weight were given metformin instead of a sulfonylurea, insulin, or conventional diet therapy. The post-trial monitoring program began once the UKPDS intervention trial was closed.

**Results**: Post-UKPDS trial risk reduction in the sulfonylurea-insulin group for myocardial infarction was 15% and 13% for death from any cause. In the metformin group, risk reduction for MI was 29% and reduction of death from any cause was 36%.
3. Thiazolidinediones (TZDs)

**PERISCOPE**: 

**Objective:** To compare the effects of pioglitazone with glimepiride on the progression of coronary atherosclerosis in patients with T2DM.

**Methods:** 543 patients were chosen, underwent coronary intravascular ultrasonography, and were then randomized to receive glimepiride 1 to 4 mg or pioglitazone 15 to 45 mg for 18 months with titration to maximum dose if tolerated. All diabetic medications patients were previously taking were permitted during the study except for a TZD, sulfonylurea, or other insulin secretagogues. Primary outcome measured was the change in percent atheroma volume from baseline. 

Re: Presence of CV disease at baseline: 
- **Inclusion:** Patients were required to have coronary angiography performed for clinical indications that demonstrated at least 1 angiographic stenosis with at least 20% narrowing. A “target vessel” for IVUS examination was required to have less than 50% obstruction throughout a 40-mm or longer segment.
- **Exclusion:** Active liver disease, or a left main coronary artery stenosis of more than 50%

**Results:** Pioglitazone was shown to slow the progression of coronary atherosclerosis in patients with diabetes. Several biomarkers indicative of atherosclerosis progression were favorably affected by pioglitazone including increase in HDL, and reductions in triglycerides and C-reactive protein levels. However, it cannot be assumed that the favorable effects found with pioglitazone are a “class effect.”

**PROactive**: 

**Objective:** PROactive was designed to investigate whether the addition of pioglitazone to the usual drug regimen of high risk type 2 diabetic patients with a history of macrovascular disease reduced mortality and macrovascular morbidity.

**Methods:** 5,238 patients with history of macrovascular disease were randomly assigned to receive either pioglitazone (n=2605) titrated from 15mg to 30mg to 45mg or placebo (n= 2633) in addition to existing therapy. The primary endpoint was the time from randomization to the first occurrence of all cause mortality, nonfatal MI, acute coronary syndrome, cardiac intervention, stroke, major leg amputation, bypass surgery, or revascularization in the leg. Secondary endpoints included time to the first event of death from any cause, myocardial infarction, stroke, cardiovascular death, or time to individual components of the primary composite endpoint.

**Results:** Study findings concluded that pioglitazone non-significantly reduces the risk of the composite primary endpoint and significantly reduced the main secondary endpoint of all-cause mortality, myocardial infarction, or stroke. Glycemic control was better in the pioglitazone group even though there was an increased use of metformin and insulin in the placebo group. There was a small increase in LDL cholesterol concentrations but decrease in total LDL in the pioglitazone group but the ratio of LDL to HDL improved more in the pioglitazone group than placebo group. There was an increased rate of edema and heart failure in the pioglitazone treated group but mortality due to heart failure did not differ between groups. To summarize, patients in the pioglitazone treated group had improved cardiovascular outcome and reduced need for insulin in addition to their glucose-lowering regimens.
Nesto et al.\textsuperscript{8} AHA/ADA Consensus Statement:

Weight gain associated with TZD use seems to be dose-dependent. It is probably due to several factors including the fact that improvement in glycemic control result in increased weight. However, fluid retention leading to weight gain is of concern with regard to cardiovascular effects. Increase in plasma volume has been noted with TZD use either as monotherapy or in combination with metformin, sulfonylurea, or insulin; however, edema is more common when the TZD is used in combination therapy. The following flow chart has been published when considering TZD therapy:\textsuperscript{8}

\textit{Note: Re: Risk factor \#2 to the right, Above evidence from PERISCOPE and PROactive suggest that this may well NOT be a risk factor for TZD use in HF, but rather a possible indication for TZD use. Rosiglitazone data is forthcoming in July 2010 which should shed some more light on the issue.}
4. Biguanides, Sulfonylureas, Meglitinides, TZDs, Alpha-Glucosidase Inhibitors, and newer compounds

Fisman et al.⁹:

**Metformin** impairs gastrointestinal absorption of folate and group B vitamins which in turn leads to increased plasma homocysteine levels resulting in vascular disease due to adverse effects on platelets, clotting factors, and endothelium. Metformin may also lead to lactic acidosis, especially in patients with conditions such as heart failure or recent myocardial infarction. Metformin undergoes renal excretion which presents potential interaction with many commonly used cardiovascular drugs such as nifedipine and furosemide.

- However, as mentioned previously, metformin has been found to have a **favorable** cardiac outcome in comparison to sulfonylureas.

The mechanism of action of **sulfonylureas** leads to its insulinotropic effects as well as the adverse effects on the heart. Sulfonylureas prevent the opening of potassium channels during ischemia, avoiding hyperpolarization that protects the cell by preventing calcium influx. Sulfonylureas have been found to reduce myocardial blood flow, impair the recovery of contractile function after ischemia, increase the ultimate infarct size, elicit proarrythmic effects, and to increase early mortality in patients with DM after direct angioplasty for acute MI.

These cardiac adverse effects are less of a concern with the second generation sulfonylureas, which were not part of the UGDP trial where most of these effects were found. In particular, glimepiride, a second generation sulfonylurea appears to be more selective to pancreas tissue and does NOT show interaction with cardiovascular ATP-dependent potassium channels. [back to quiz]

**Meglitinides** can be thought of as “short acting sulfonylureas.” Their cardiovascular impact is unclear; however their mechanism of action involves the prevention of potassium channels which may lead to the same adverse effects as the sulfonylureas.

**TZDs** have been shown to decrease leptin levels, leading to weight gain. Rosiglitazone may be linked to increased risk of myocardial infarction and increase risk of death from cardiovascular causes. It has been debated whether rosiglitazone should remain on the market yet the FDA has chosen to keep it on the market until there is more sufficient evidence as more recent literature suggests rosiglitazone is safer than previously thought. Both TZDs are contraindicated in NYHA class III or IV. The risk of heart failure is a class effect; however, at present the risk of ischemia appears confined to rosiglitazone. Pioglitazone reduces LDL while rosiglitazone appears to raise it.

**Acarbose** is the most widely studied **alpha-glucosidase inhibitor**. It has been shown to reduce hypertension and cardiovascular disease. The STOP-NIDDM trial found acarbose to have a 34% risk reduction in the development of new cases of hypertension, and a **49% risk reduction in cardiovascular events**.

Regarding newer compounds, **exenatide (Byetta)** may be associated with an increase in stroke volume and cardiac output as well as decreased in left ventricular end-diastolic volume as seen in experimental studies where GLP-1 receptors have been noted in cardiac myocytes and regions of the brain that regulate autonomic function.

There isn’t much data on the cardiovascular impact of **DPP4 inhibitors**, but they appear to be neutral and do not cause weight gain. **Pramlintide** has not been associated with cardiovascular advantages or risks.
5. Intensive Glucose Therapy and Cardiovascular Outcomes

**VADT**<sup>10</sup>:

Background: This trial was completed in order to determine the effects of intensive glucose control on cardiovascular events in patients with long-standing type 2 diabetes mellitus.

Methods: 1791 military veterans with a mean age of 60.4 years with a history of suboptimal T2DM control were randomly assigned to receive either intensive or standard glucose control. The mean duration of time since diagnosis of T2DM was 11.5 years and 40% of the patients had already had a cardiovascular event.

In both study groups, patients with a BMI ≥ 27 were started on metformin plus rosiglitazone and those with a BMI ≤ 27 were started on glimepiride plus rosiglitazone. Patients in the intensive therapy group were given the maximal doses and patients on standard therapy were given half the maximal doses. Insulin was added to the regimen for patients in the intensive therapy group who did not achieve an A1C less than 6% and to patients in the standard therapy group who did not achieve an A1c less than 9%. Any further changes in medication regimen for either group was up to the discretion of the provider and use of any approved drug was allowed. The goal was an absolute reduction of 1.5% in the intensive therapy group as compared to the standard therapy group.

The primary outcome was the time to first occurrence of myocardial infarction, stroke, death from cardiovascular causes, new or worsening congestive heart failure, surgical intervention for cardiac, cerebrovascular, or peripheral vascular disease, inoperable coronary artery disease, and amputation for ischemic gangrene. Secondary outcomes included new or worsening angina, new transient ischemic attacks, new intermittent claudication, new critical limb ischemia, death from any cause, and microvascular complications.

Results: After intensive therapy, A1C level was 6.9%, and 8.4% after standard therapy. There was NO decrease in cardiovascular complications and the rates of weight gain and hypoglycemia were greater in the intensive therapy group.

**ADVANCE**<sup>11</sup>:

Background: The purpose of the ADVANCE trial was to determine the effects of intensive glucose control on vascular outcomes.

Methods: 11,140 patients with T2DM were divided into two groups- one of which received standard glucose control (not with gliclazide modified release) and the other to receive intensive glucose control (gliclazide modified release, 30 to 120 mg daily plus other drugs as required to achieve an A1c ≤ 6.5%), with all other medications used at the discretion of the treating physician. Participants were diagnosed with T2DM at age 30 or older, were at least 55 years of age, and had a history of major macrovascular OR microvascular disease OR at least one other risk factor for vascular disease.

The primary endpoints were macrovascular events including death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke as well as microvascular events including new or worsening nephropathy or retinopathy. Secondary endpoints included death from any cause, death from cardiovascular causes, major coronary events, total coronary events, major cerebrovascular events, total
cerebrovascular events, heart failure, peripheral vascular events, all cardiovascular events, new or worsening nephropathy, new or worsening retinopathy, development of microalbuminuria, visual deterioration, new or worsening neuropathy, decline in cognitive function, dementia, and hospitalization for 24 hours or more.

Results: Intensive glucose control significantly reduced the primary composite outcome of major macrovascular OR microvascular events, mainly as a consequence of reduction in nephropathy. There was NOT separate significant reduction in macrovascular events, yet a modest benefit could NOT be ruled out.

**ACCORD**:  

Background: Whether intensive therapy to target normal A1C levels would reduce cardiovascular events in patients with T2DM who had either established cardiovascular disease or additional cardiovascular risk factors was investigated.

Methods: 10,251 randomized patients were assigned to either intensive therapy (goal A1C < 6.0%) or standard therapy (goal A1C 7.0% to 7.9%). 35% of subjects had had a previous cardiovascular event. In addition, 4733 of these patients were assigned to lower their blood pressure with intensive therapy or standard therapy, and 5518 were assigned to receive fenofibrate or placebo while maintaining LDL with simvastatin.

Therapeutic regimens with regard to glucose control were at the discretion of the provider.

Primary endpoints included the first occurrence of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes. Secondary outcomes included death from any cause, the effect of any intervention on microvascular disease, hypoglycemia, cognition, and quality of life.

Results: The finding of higher mortality (22%) in the intensive therapy group led to the discontinuation of the trial after an average of 3.5 years of follow up. Since the standard therapy group had fewer study visits and used fewer drugs, the higher rate of death in the intensive therapy group may be due to the strategies of blood glucose reduction.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Subjects (mean age)</th>
<th>Patient Type</th>
<th>Description</th>
<th>A1C Intense vs. Standard</th>
<th>Results</th>
</tr>
</thead>
</table>
| UKPDS | 3867 (54 years)     | T2DM – new onset | 10 yr follow up of standard vs. intense treatment | 7.0% vs. 7.9% | Intensive blood glucose control decreases the risk of microvascular, but NOT macrovascular complications  
  - MI (16.5 vs. 14.2%)  
  - Fatal MI (4.4 vs. 7.59%)  
  - Stroke (4.8 vs. 5.4%)  
  - Fatal Stroke (1.3 vs. 1.6%) |
| UKPDS – 10-year Follow Up | 3,277 | T2DM – previously in UKPDS trial, completing post-trial follow up | Post-UKPDS trial follow up to determine whether intensive glucose control had persisted and whether it had long-term effects on macrovascular outcomes |  | Reduction of microvascular events was sustained throughout post-trial follow up. Reduction of macrovascular events in the sulfonylurea-insulin group:  
  - MI: 15%  
  - Death from any cause: 13%  
  Metformin group:  
  - MI: 39%  
  - Death from any cause: 36% |
| ACCORD | 10,251 (62.2 yrs) | T2DM-avg duration of DM was 10 years, median baseline A1C 8.1% | 3.5 yr follow up of standard vs. intensive treatment  
  Note: stopped early due to increase CV risk in intensive treatment group | 6.4 vs. 7.5% | No significant effects of the type of control on major macrovascular events:  
  - Non-fatal MI (4.6 vs. 3.6%)  
  - Nonfatal stroke (1.2 vs. 1.3%)  
  - CV-related death (1.8 vs. 2.6%) |
| ADVANCE | 11, 140 (66.0 yrs) | T2DM- avg duration of DM was 8 years, avg baseline A1C was 7.5% | 5 yr follow up of standard vs. intensive treatment | 6.5 vs. 7.3% | No significant effects of the type of control on major macrovascular events  
  - Nonfatal MI (2.8 vs. 2.7%)  
  - Nonfatal stroke (3.8 vs. 3.8%)  
  - CV-related death (5.2 vs. 4.5%) |
| VADT | 1,791 (60.4 yrs) | T2DM- Avg duration of DM was 11.5 years, avg baseline A1C was 9.4% | 5.6 yr follow up of standard vs. intensive treatment | 6.9 vs. 8.4% | No significant effects of the type of control on major macrovascular events:  
  - Nonfatal MI (8.7 vs. 7.2%)  
  - Nonfatal stroke (4.0 vs. 3.2%)  
  - CV-related death (3.2 vs. 4.3%) |
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>CV Impact</th>
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<tbody>
<tr>
<td>Sulfonylureas</td>
<td><strong>Stimulate pancreatic beta-cells to increase insulin release</strong></td>
<td>Conflicting evidence: UGDP trial found that SU’s worsen ischemia yet UKPDS 10-yr follow up study found SU’s do not affect macrovascular complications and in fact reduced cardiac complications during post-trial follow up</td>
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</table>
| Biguanides                 | **Decreases hepatic gluconeogenesis production**  
|                           | **Decreases intestinal absorption of glucose**  
|                           | **Increases peripheral glucose uptake and utilization**                                                                                                                                                                                                                                                                                                                                                                                                                               | Improved glucose control with metformin has been found to reduce cardiovascular events. Metformin may interfere with the elimination of cardiovascular drugs that undergo renal excretion                                                                                   |
| Alpha-Glucosidase Inhibitors | **Inhibits alpha-glucosidases present in the brush border of the enterocytes of the small intestine thereby delaying carbohydrate digestion and absorption**                                                                                                                                                                                                                                                                          | Found to reduce risk of hypertension and cardiovascular disease.                                                                                                                                                                                                                     |
| Thiazolidinediones         | **Enhancement of insulin sensitivity in adipose tissue, skeletal muscle, and the liver**                                                                                                                                                                                                                                                                                                                                                                                                               | Rosiglitazone poses a risk of ischemia, MI, and death due to CVD. Both rosiglitazone and pioglitazone are associated with risk of heart failure exacerbation (particularly stage III and IV). Rosiglitazone tends to increase LDL, pioglitazone decreases LDL, has been shown to decrease incidence of MI and stroke, as well as slow the progression of coronary atherosclerosis |
| Meglitinides               | **Stimulates insulin secretion from pancreatic beta-cells (short acting)**                                                                                                                                                                                                                                                                                                                                                                                                                      | Unclear, similar mechanism of action as SU’s, therefore similar CV impact may be present                                                                                                                                                                                                         |
| Insulin                    | **Promotes storage and inhibits breakdown of glucose, fat, and amino acids**  
|                           | **Facilitates uptake of glucose in muscle and adipose tissue and inhibits glycogenolysis and gluconeogenesis**  
|                           | **Enhances lipogenesis**  
|                           | **Increases protein synthesis and inhibits proteolysis**                                                                                                                                                                                                                                                                                                                                                                                                                                 | In vitro studies have linked hyperinsulinemia to atheroma and myocardial infarction. UKPDS disputes this noting intense glucose control does not affect macrovascular complications in T2DM, however; UKPDS 10-yr follow up study, suggested that significant decrease to MI’s results from intense glucose control. |
| Incretin Mimetics          | **Binds and activates glucagon-like peptide-1 thereby increasing insulin synthesis and secretion**  
|                           | **Suppresses glucagon secretion, slows gastric emptying, promotes beta cell proliferation (increases release of insulin in the presence of elevated glucose concentrations only)**                                                                                                                                                                                                                                                                 | May result in increased stroke volume and cardiac output as well as decreased left ventricular end-diastolic volume. More data is needed but weight reduction is likely to provide some CV benefit.                                                                 |
| DPP4-Inhibitors            | **Inhibits dipeptidyl peptidase-IV which inactivates incretin hormones**                                                                                                                                                                                                                                                                                                                                                                                                                       | Not enough data available yet. Januvia is weight neutral.                                                                                                                                                                                                                                 |
| Amylin Analogs             | **Slows gastric emptying, suppresses postprandial glucagon secretion, and centrally modulates appetite**                                                                                                                                                                                                                                                                                                                                                                                                                                      | Pramlintide has not been associated with cardiovascular advantages or risks, however weight reduction is likely to provide some CV benefit.                                                                                                                                                                           |
Cardiovascular disease is the main cause of death in diabetic patients. Improved blood-glucose has been shown to decrease the progression of microvascular disease, but there is less evidence regarding benefit to macrovascular disease. The results of the ACCORD, VADT, ADVANCE, and UKPDS 10-yr follow up trials suggest that tight glucose control does not reduce macrovascular complications in diabetic patients. Notably, the ACCORD trial was terminated early due to higher mortality in the intensive treatment group. During the UKPDS study, patients with T2DM who received intensive glucose therapy had a lower risk of microvascular complications. Post trial monitoring was done to determine whether such therapy had long-term effect on macrovascular outcomes. It was found that among the groups treated (sulfonylurea, insulin, or metformin); those on sulfonylurea or insulin had a 25% reduction in the risk of microvascular disease during the trial and throughout the post-trial period. Decreased risk of macrovascular complications in these treatment groups was not observed during the trial, but post-trial risk reductions were found to be 15% for myocardial infarction and 13% for death from any cause. Whether the patients taking sulfonylurea during the trial were switched to metformin after UKPDS trial results were concluded is of question since this may have contributed to the reduction in risk of macrovascular events during the post-trial follow up. In the metformin group, reductions for myocardial infarction (39%) and death from any cause (36%) were observed during the original trial as well as throughout the post-trial period. The mechanism behind this may be that gradual accumulation of advanced glycation end products are slowly degraded by intensive glucose control. The positive effects of this are seen first in reducing microvascular complications followed by a lag phase before reductions in macrovascular complications are seen. In contrast, the mechanism of action behind many oral antidiabetic drugs has direct effects on the cardiovascular system. A summary of the article by Fisman, et al:

- Biguanides, Thiazolidinediones, Sulfonylureas, and meglitinides present proven or potential hazards to various types of cardiovascular risks
- These hazards are related to the mechanism of action of each class of drugs, not merely a “side effect.”
- Glyburide/metformin appears to have an increased cardiac risk potential and should be avoided in patients with known CAD
- TZDs are contraindicated in patients with NYHA Class III or IV
- Incretin mimetics and DPP-4 inhibitors appear to be safe with regard to cardiovascular adverse effects, but further study is needed on these newer agents.
- Customized pharmacological approach should be taken when treating T2DM patients with heart disease. Whether it is heart failure or CAD should be noted and taken into consideration.

TZDs have been found to exacerbate heart failure, even though certain studies have found rosiglitazone to have no effect on LVEF. However, many studies performed on the relationship between rosiglitazone and CV effects have been funded by GlaxoSmithKline. The risk of cardiac complications due to the mechanism of each drug must be weighed against the advantages of long-term tight glucose control which has been shown to reduce microvascular complications followed by macrovascular complications.

**Conclusion**

The UKPDS trial found improved glycemic control reduced risk of microvascular disease during trial but reduced risk of macrovascular complications were only observed during post-trial follow up. UKPDS studied patients with new diagnosis of T2DM and found that intensive glucose control at the time of diagnosis is associated with a decreased risk of MI and death from any cause in addition to the already-known advantages of
reduction in microvascular complications\(^4\). Per Fisman et al, glyburide/metformin should be avoided or at least used for only a short period in patients with CAD\(^7\). TZDs should not be used in heart failure patients Class III or IV.\(^9\) A customized therapy of combined anti-diabetic agents should be implemented in T2DM patients without known contraindications as tight glucose control exhibits long-term benefits including reduction in macrovascular complications. The mechanisms behind the cardiac complications related to anti-diabetic drug classes are biochemical phenomena derived from their mechanism of action, yet in most cases, the benefits of long term glucose control outweigh the risk of these adverse effects.

**Quiz Answers:**
1. A
2. C
3. A
4. A
5. A
6. A

**References**