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# Prevention and Treatment of Diabetes-related Cardiovascular Complications

*The rise in the incidence of obesity and diabetes threatens the recent successes we have had in the United States in fighting heart disease. This issue provides practical insights into strategies that the primary care physician can employ to address the risk of cardiovascular complications in the diabetic patient.*

*—The Editor*

## Case Study

Dan, a 46-year-old Caucasian male, was discharged from the hospital one week ago after sustaining a myocardial infarction (MI) during admission for chest pain. His blood pressure upon admission was 154/92 mmHg; fasting glucose was 363 mg/dL; total cholesterol was 285 mg/dL; low density lipoprotein-cholesterol (LDL-C) was 180 mg/dL; triglyceride (TG) was 466 mg/dL; and high density lipoprotein-cholesterol (HDL-C) was 25 mg/dL. He was diagnosed with coronary artery disease (CAD), hypertension, type 2 diabetes, and hyperlipidemia. He had percutaneous intervention with stents placed in two vessels. He came into the hospital on no medications and thinking he was well. Now he has a list of problems and eight new medications, including insulin. He has been a smoker for more than 30 years and has not exercised since he played football in high school. He has a very strong family history of type 2 diabetes and heart disease. Very few of the males in his family have lived past the age of 55 due to significant heart disease.

In 2007, 23.6 million people, or 7.8% of the population in the United States had diabetes.[1] Currently, death from cardiovascular disease (CVD) is estimated to occur in 80% or 18.4 million of those Americans.[1] Many patients, like Dan in the case study, are not diagnosed with type 2 diabetes until a cardiovascular event has already occurred. Approximately 30% of patients with an acute MI are newly diagnosed with type 2 diabetes prior to hospital discharge.[2]

Diabetes already costs the U.S. population $174 billion a year in direct and indirect expenses.[1] It has been estimated that 1 in 5 U.S. Medicare dollars are spent on persons with diabetes.[3] Diabetes, its projected expansion, and its complications could cripple the economy of our health care system. Unfortunately, we are currently only observing the tip of the iceberg.

Type 2 diabetes not only affects the adult population but is becoming increasingly more common in children and adolescents. Almost 4000 young people are diagnosed with type 2 diabetes annually,[1] and the CDC estimates that one in every three Americans born in the year 2000 will eventually develop type 2 diabetes.[1] This will lead to even more cardiovascular complications at a much earlier age.

## Pathophysiology

Atherosclerosis is the underlying pathological lesion that leads to

## Executive Summary

- Diabetics have a 2-4 times increased risk of suffering a cardiovascular event.
- The most effective approach in reducing that risk is by addressing, in order of decreasing importance, blood pressure control, hyperlipidemia, and hyperglycemia.
- In a *Lancet*-published meta-analysis of trials involving more than 33,000 patients, intensive glucose control resulted in a 17% reduction in nonfatal MI and a 15% reduction in coronary heart disease but no significant differences in stroke or all-cause mortality.

macrovascular events. Atherosclerosis is a buildup of plaque in the arteries initiated by chronic inflammation and injury to the arterial wall. Endothelial injury and inflammation lead to monocyte and lipid infiltration into the endothelial wall with subsequent foam cell formation. Foam cells, in turn, stimulate macrophage proliferation and T lymphocytes, causing smooth muscle proliferation and collagen formation. Finally, a lipid-rich atherosclerotic lesion with a fibrous cap is formed. Rupture of this will then lead to an acute vascular infarct.[4]

Patients with diabetes have a two- to four-fold increased risk of having a cardiovascular event.[1] Atherosclerotic lesions and macrovascular events are increased even in patients with impaired fasting glucose and impaired glucose tolerance.[5] In addition to the usual risk factors associated with atherosclerosis, type 2 diabetes and pre-diabetes contribute additional and unique factors, including hyperglycemia, insulin resistance, and inflammation.

Insulin resistance occurs when normal levels of insulin fail to trigger signaling for glucose absorption into peripheral tissues. Beta-cell hypertrophy and hyperplasia allows for increased insulin secretion from the pancreas to maintain euglycemia. Over time, the beta cell is overwhelmed, glucose-stimulated insulin secretion is impaired, and hyperglycemia ensues. The lack of insulin response leads to a state of increased catabolism. Increased hepatic gluconeogenesis, lipolysis of adipose tissue, and breakdown of protein occurs, resulting in increased blood glucose, circulating free fatty acids (FFA), and lactate levels, respectively. The normal protective mechanisms of insulin, including vasodilatory and anti-inflammatory properties, are diminished as well.[6]

Adipose tissue also plays a role as an active endocrine organ with the release of a large number of cytokines. Excess adipose tissue from obesity contributes to increased release of FFA with subsequent alteration in the release of inflammatory cytokines. Consequently, there is an increase in pro-inflammatory cytokines, including: leptin, plasminogen activator inhibtor-1 (PAI-1), angiotensinogen, resistin, interleukin-6 (IL-6), interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), p-selectin, vascular cell adhesion molecule-1 (VCAM-1), and fibrinogen. Adioponectin, an anti-inflammatory cytokine, is suppressed.[7]

Initiation of these processes in diabetic patients is believed to be due to overproduction of superoxide by the mitochondrial electron transport chain. In macrovascular disease, the proposed trigger is increased FFA flux from adipocytes, resulting in FFA oxidation by the mitochondria and mitochondrial overproduction of reactive oxygen species (ROS). This leads to activation of the polyol pathway, increased advanced glycation end products (AGE), activation of the protein kinase C (PKC) pathway, and upregulation of the hexosamine pathway.[8] The combination of these pathways causes disruption in insulin signaling, impaired vasodilation (decrease nitric oxide), increased oxidative stress (reactive oxygen species), and high levels of FFA, vasoconstrictors (enodthelin-1), cellular adhesion molecules, anti-fibrinolytics (PAI-1), cytokines (TNF-alpha, IL-1, IL-6, interleukin-8, monocyte chemoattractant protein-1), and other mediators of low-grade inflammation and thrombosis formation.[9] Inflammatory cytokines produced by these processes induce further insulin resistance and attract macrophages to the adipose tissue, creating a constant cycle for a chronic inflammatory state.

### Current Risk Factor Reduction Targets

Risk factor reduction is the most important therapy for primary and secondary prevention of macrovascular disease in patients with diabetes. The greater the number of risk factors, the greater the overall risk of macrovascular disease.[10] Risk factor reduction includes lifestyle management, blood pressure control, lipid management, glucose control, tobacco cessation, and antiplatelet therapy.

The most effective approach to decreasing cardiovascular mortality is to address hypertension first, then hyperlipidemia, and finally glucose control.[11] Recommended treatment goals for these risk factors are listed in Table 1. Blood pressure and LDL-C goals have been established based on large prospective randomized controlled trials.[12-19] However, the independent role of intensive glucose control in the reduction of macrovascular disease has never been proven in a large prospective randomized controlled trial. Goals for A1c were established based on evidence linking a reduction in microvascular, not macrovascular, outcomes to A1c values of < 7%.[20-22]

***Table 1:*** Cardiovascular Risk Reduction Targets in Patients with Diabetes[23]

| | Goal |
|---|---|
| A1c | < 7.0% (ADA and ACP)<br>< 6.5% (AACE and IDF) |
| Blood pressure (ADA) | < 130/80 mmHg |
| LDL-C (ADA) | < 100 mg/dL very high risk<br>< 70 mg/dL highest risk |
| HDL-C (ADA) | > 40 mg/dL (men)<br>> 50 mg/dL (women) |
| Triglyceride (ADA) | < 150 mg/dL |
| * American Diabetes Association (ADA), American College of Physicians (ACP), American Association of Clinical Endocrinologists (AACE), International Diabetes Federation (IDF) | |

The importance of blood pressure and cholesterol control cannot be understated but will not be discussed further here as it is beyond the scope of this paper. The remainder of this review will look at the recent literature on the influence of glucose control on cardiovascular disease.

## Previous Glucose Trials

The Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study Group (UKPDS) trials are landmark studies in the evaluation of glucose control and its effects on microvascular and macrovascular complications.

More than 1400 patients with type 1 diabetes were evaluated in the DCCT trial. Newly diagnosed patients were randomized to either intensive glucose control (multiple daily insulin injections or insulin pump) or standard therapy (one or two insulin injections daily) and underwent intervention for 6.5 years. A statistically significant reduction in risk of retinopathy (54-76%), nephropathy (50%), and neuropathy (60%) was noted with intensive versus standard glucose control. There was also a 41% reduction in major cardiovascular and peripheral vascular disease in the intensive therapy group, but this was not statistically significant.[22] However, a significant benefit was noted in the 10-year observational follow-up of the DCCT. The Epidemiology of Diabetes Interventions and Complications (EDIC) trial found a 42% reduction in risk of heart disease and a 57% reduction in risk for nonfatal myocardial infarction (MI), stroke, or death from CVD despite similar glucose control after observation period.[22]

In type 2 diabetes, the UKPDS trial evaluated more than 5000 patients. Newly diagnosed patients were randomized to either intensive glucose control (sulfonylurea and insulin or metformin) or conventional therapy (dietary therapy) and were followed for 10 years. Microvascular complications were reduced by about 25% with intensive glucose control. A non-significant 16% reduction in risk of combined fatal or nonfatal MI and sudden death was noted in the intensively treated group. There was also a trend toward an 18% reduction in combined fatal and nonfatal MI for every 1% decrease in HbA1c with no glycemic threshold.[20] In the 10-year follow-up results of the UKPDS trial, despite a convergence of A1c values one year after the end of the intervention, a significant risk reduction in myocardial infarction (15%) and death from any cause (13%) emerged, much like what was seen in the EDIC trial.[24]

These studies suggest that early intensive treatment of hyperglycemia may have long-lasting effects that decrease risk for macrovascular complications, the so-called "legacy effect."

As mentioned previously, glucose targets have been recommended largely due to these landmark trials (DCCT and UKPDS) and their role in prevention of microvascular disease. Observational data in the EDIC and UKPDS trials suggest a cardiovascular benefit from intensive glucose control in patients with type 1 and type 2 diabetes. However, this benefit still has not been observed in a prospective trial. Therefore, three recent large prospective randomized trials have been completed to investigate the role of intensive glucose control in prevention of macrovascular disease and mortality in patients with type 2 diabetes. (*See Table 2.*)

## Current Glucose Trials

The Action to Control Cardiovascular Risk in Diabetes (ACCORD), the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and the Veterans Affairs Diabetes Trial (VADT) looked at cardiovascular risk and mortality in patients with type 2 diabetes. These studies found either no benefit or an increase in cardiovascular mortality with intensive vs. conventional glucose targets.

The ACCORD trial evaluated cardiovascular outcomes in more than 10,000 patients with type 2 diabetes and either a history of a cardiovascular event or significant cardiovascular risk (age 55-79, angiographical CVD, albuminuria, left ventricular hypertrophy) or at least two other CVD risk factors. Multiple combinations of oral therapies and insulin were used to obtain a target A1c of < 6% vs. 7-8%.[25] The intensive glucose arm was stopped prematurely at 3.5 years due to an increase in all-cause mortality associated with the intensively treated group. There were 257 deaths (5%) in the intensively treated group vs. 203 deaths (4%) in the conventional group.[25] Patients in the intensively treated group had more combinations of medications, increased use of insulin, increased weight gain, and a higher frequency of severe hypoglycemia compared to the standard therapy group. In

***Table 2:*** Cardiovascular Risk Reduction in the DCCT, EDIC, UKPDS, and UKPDS 10-year Follow-up Trials[21,22,24]

| Trial | DCCT* | EDIC*† | UKPDS*** | UKPDS 10 yr*** |
|---|---|---|---|---|
| Participants (number) | 1,441 | 1,357 | 5,102 | 1,525 |
| Duration intervention | 6.5 years | | 10 years | |
| Mean age | 27 years | | 54 years (S/I)<br>53 years (M) | |
| Mean duration diabetes | Newly diagnosed | | Newly diagnosed | |
| Intensive intervention | Insulin pump or multiple daily injections | | Sulfonylurea and insulin or metformin | |
| Conventional intervention | One or two daily insulin injections | | Dietary therapy | |
| Median A1c<br>• Intensive | 7.4% | 7.9% | 7.0% (S/I)<br>7.4% (M) | 7.9% (S/I)<br>8.4% (M) |
| • Conventional | 9.1% | 9.1% | 7.9% (S/I)<br>8.0% (M) | 8.5% (S/I)<br>8.9% (M) |
| Hypoglycemia rate<br>• Intensive | 62 per 100 patient years | | 0.6-2.3% (S/I) | |
| • Conventional | 19 per 100 patient years | | 0.1% (S/I) | |
| Primary outcome | 41% reduction major cardiovascular and peripheral vascular disease** | 42% reduction heart disease; 57% reduction nonfatal MI, stroke, death from CVD | 16% reduction fatal and nonfatal MI and sudden death | 15% reduction MI and 13% reduction death from any cause |

S/I, sulfonylurea and insulin group, M, metformin group;
*Major trial in type 1 diabetes mellitus
**Not statistically significant
***Results on primary outcome are based on combined sulfonylurea/insulin and metformin groups. Metformin had additional benefits with reduction in MI (39%) and death from any cause (36%).
†Both EDIC and the UKPDS 10-year follow-up are epidemiological studies and no intervention was done for these.

sub-analyses, the ACCORD group could not explain the excess mortality in the intensive arm by weight gain, hypoglycemia, or any combination of medications.[25]

A non-significant decrease in the primary outcome (composite of nonfatal MI, nonfatal stroke, or death from cardiovascular cause) was found in the intensively treated group (6.9%) vs. standard therapy (7.2%) (p = 0.16). This was mainly due to a statistically significant decrease in nonfatal MI in the intensively treated group vs. standard therapy of 3.6% and 4.6%, respectively (p = 0.004).[25] Additional arms of the trial looking at blood pressure control and use of fibrates plus statins for lipid reduction are still ongoing.

The ADVANCE trial included more than 11,000 patients with type 2 diabetes older than age 55 with either a history of vascular disease or at least one other vascular risk factor besides diabetes. Gliclizide, a sulfonylurea, was the primary therapy for all patients in the study. Investigators used different oral medications and insulin to obtain either an intensive glucose target (A1c < 6.5%) or the "usual" glucose target. The primary outcome was a composite of major macrovascular events (death from cardiovascular causes, nonfatal MI, or nonfatal stroke) and microvascular events (new or worsening nephropathy or retinopathy). A significant reduction in the primary outcome was found in the intensive therapy group (18.1% vs. 20.0%; p = 0.01). However, this outcome was mainly due to a reduction in nephropathy of 4.1% vs. 5.2%, respectively (p = 0.006). No significant reduction

in macrovascular events was noted between the two different glycemic target groups ($p = 0.32$).[26]

The VADT also evaluated intensive glucose control on cardiovascular outcomes in patients with type 2 diabetes. More than 1700 military veterans with type 2 diabetes uncontrolled on insulin or maximal dose oral agents were assigned to either intensive (A1c < 7%) or standard (A1c 8-9%) glucose control. The primary outcome was time from randomization to the first occurrence of a major cardiovascular event, a composite of myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene. No significant difference was found in the primary outcome between the two treatment groups (29.5% vs. 33.5%; $p = 0.14$).[27] Initially, there was no significant improvement in microvascular outcomes. However, after re-analysis, a statistically significant improvement in micro-albuminuria was found with intensive therapy ($p < 0.01$).[28]

## Meta-analyses of Landmark Glucose Trials

Meta-analyses of the ACCORD, ADVANCE, VADT, and UKPDS trial were recently completed in which data from more than 27,000 patients were evaluated. The primary outcome was death from cardiovascular causes (sudden death, nonfatal MI, and nonfatal stroke). A reduction in the primary outcome was noted in the intensive vs. the standard group over a 4.4-year period (9%). This was mainly due to a decrease in nonfatal MI (15%). There was a small, non-significant trend toward an increase in all-cause mortality in the intensively treated patients (hazard ratio [HR] 1.04). Patients without a previous cardiovascular event benefited more from tight control (HR 0.84) compared to patients with a previous cardiovascular event (HR 1.0).[29]

*The Lancet* published data from a meta-analysis including the UKPDS, PROactive, ACCORD, ADVANCE, and VADT trials evaluating more than 33,000 patients. The primary outcome was nonfatal MI, coronary heart disease (combined fatal and nonfatal MI), stroke, and all-cause mortality. Mean A1c was 0.9% lower in the intensively treated patients. Intensive glucose control was associated with a 17% reduction in nonfatal MI and a 15% reduction in coronary heart disease. No significant differences were found in stroke or all-cause mortality.[30]

## Comparison of Trials

The DCCT and UKPDS trials included patients who were at least 10 years younger, were newly diagnosed versus having diabetes for approximately 10 years, and had fewer comorbidities than the ACCORD, ADVANCE, or VADT trials.

Of note, even though there was no significant difference in cardiovascular events in ADVANCE and VADT, there was a slight trend toward cardiovascular benefit toward the end of the trials. The only data available for the ACCORD, ADVANCE, and VADT trials has been over the intervention period of 3.4-5.6 years. The DCCT/EDIC and the UKPDS did not show any significant reduction in cardiovascular risk until their observational follow-up 10 years later. It has been suggested that patients from ACCORD, ADVANCE, and VADT be followed observationally as well, and it remains to be seen if they will also show the "legacy effect" that was found in the follow-up trials of DCCT/EDIC and UKPDS.

There also are differences between the three recent trials. Some of these variables may account for the increased mortality in the ACCORD trial that was not seen in ADVANCE or VADT. Patients in the ADVANCE trial had a shorter duration of diabetes by about 2 years, lower baseline A1c values, and were taking fewer medications than the participants in the ACCORD trial. No increase in mortality was noted in the VADT as compared to ACCORD despite a longer duration of diabetes and an increased incidence of baseline cardiovascular disease in VADT patients. One explanation for this is that less intense therapy was achieved in VADT compared to ACCORD. This further emphasizes the point that tighter glucose control may not be appropriate for older patients with a high cardiovascular risk. Of note, control of other cardiovascular risk factors and use of proven medications were utilized less often in the ADVANCE trial in comparison to the ACCORD or VADT trials.

## Explanation Beyond A1c for Increased Mortality: Hypoglycemia

Severe hypoglycemia has been proposed as part of the explanation for the increased mortality in the ACCORD trial. Hypoglycemia stimulates the sympathetic nervous system and increases catecholamines that will increase heart rate, blood pressure, and oxygen demand on the heart. Also, stress on the arterial wall may contribute to plaque destabilization and rupture.[31] Severe hypoglycemia in the ACCORD trial was recorded based on self-report of a blood sugar less than 50 mg/dL that required assistance. Events with blood sugars between 50-70 mg/dL and those that did not require assistance were not recorded. Hypoglycemic events were documented in 16% of the intensively treated group versus 5% in the conventionally treated group.[25] Patients with at least one episode of severe hypoglycemia had a higher risk of death in both the intensive and conventional control groups. Interestingly, the risk of death was lower among the patients in the intensive treatment arm (HR 1.4) compared to the standard treatment arm (HR 2.3). Nineteen of the 41 excess deaths due to cardiovascular disease in the intensive group were attributed to unexpected or presumed cardiovascular disease.[25] Death from cardiovascular disease may have been mistakenly attributed and could have been from a hypoglycemic event due to lack of good blood glucose measurements and

***Table 3:*** Comparison of Characteristics in ACCORD, ADVANCE, VADT[25-27]

| Trial | ACCORD | ADVANCE | VADT |
|---|---|---|---|
| Participants (number) | 10,251 | 11,140 | 1,791 |
| Duration intervention | 3.4 years | 5.0 years | 5.6 years |
| Mean age | 62.2 years | 66.0 years | 60.4 years |
| Mean duration diabetes | 10 years (median) | 7.9 years | 11.5 years |
| Mean baseline A1c | 8.3% | 7.5% | 9.4% |
| Previous cardiovascular event | 35.2% | 32.2% | 40.2% |
| Intervention | At least 2 hypoglycemic agents plus other drugs | Gliclazide plus other drugs | Glimiperide or metformin, plus rosiglitazone, or insulin |
| Control | Diet or pharmacologic treatment or both | Current therapy | Glimiperide or metformin plus rosiglitazone or insulin |
| Median A1c** | 6.2% vs. 7.2% | 6.3% vs. 7.0% | 7.1% vs. 8.5% |
| Severe hypoglycemia** | 16% vs. 5% | 2.7% vs. 1.5% | 24.1% vs. 17.6% |
| Insulin** | 77% vs. 55% | 40% vs. 24% | 89% vs. 74% |
| TZD** | 91% vs. 58% | 17% vs. 11% | 53% vs. 42% |
| Sulfonylurea** | 78% vs. 68% | 92% vs. 59% | |
| Metformin** | 94% vs. 87% | 74% vs. 67% | |
| Statin** | 88% vs. 88% | 46% vs. 48% | 85% vs. 83% |
| Aspirin** | 76% vs. 76% | 57% vs. 55% | 88% vs. 86% |
| BP (mmHg)** | 126/67 vs. 127/68 | 136/74 vs. 138/74 | 127/68 vs. 125/69 |
| LDL-C** | 91 mg/dL | 102 mg/dL | 80 mg/dL |
| Weight change (kg) | 3.5 vs. 0.4 | -0.1 vs. -0.1 | 7.8 vs. 3.4 |
| Primary outcome | 6.9% vs. 7.2% (HR 0.90) (p = 0.16) | 10.0% vs. 10.6% (HR 0.94) (p = 0.32)*† | 29.5% vs. 33.5% (HR 0.88) (p = 0.14)* |

HR = hazard ratio
* Not statistically significant
† Major macrovascular events only. There was a statistically significant primary outcome with the combination of macrovascular and microvascular events (18.1% vs. 20.0%; p = 0.01) with intensive therapy.
** Intensive vs. conventional therapy at the end of the study period.

no anatomic features of hypoglycemia postmortem.[28] However, the ACCORD group noted that severe hypoglycemia could not fully explain the excess mortality.

In the VADT trial, there also were more frequent severe hypoglycemic events in the intensively treated group (24.1% vs. 17.6%). In this study, severe hypoglycemia within 90 days was a strong predictor of the primary outcome and cardiovascular mortality. Similar to the ACCORD trial, severe hypoglycemia was associated with all-cause mortality only in the standard treatment arm.[27] This suggests that patients experiencing hypoglycemia in the standard group had higher glycemic variability with a greater difficulty in reaching target blood glucose levels. In light of this, these patients may be at a disproportionately increased risk for hypoglycemia and mortality.

## Explanation Beyond A1c for Increased Mortality: Medication Selection

As with hypoglycemia, different combinations of medications independently could not account for the increase in mortality seen in the ACCORD trial. However, in previous studies, specific therapies have shown different risk profiles for cardiovascular disease and mortality.

Since the 1970s, there have been reports of a possible increased risk of cardiovascular mortality with sulfonylureas.[32] Sulfonylureas work by blocking the potassium ATP channel located on the beta cells of the pancreas to allow for increased release of insulin. The myocardium also has

***Table 4:*** Primary Outcomes in the ACCORD, ADVANCE, and VADT[25-27]

| Trial | Outcomes | Outcomes Met |
|---|---|---|
| ACCORD | Composite of nonfatal MI, nonfatal stroke, or death from cardiovascular causes | Yes* |
| ADVANCE | Composite of major macrovascular events (death from cardiovascular causes, nonfatal MI, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy) | Yes** |
| VADT | Composite of major macrovascular events (MI, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular causes, inoperable coronary disease, and amputation for ischemic gangrene) | No |

*** The primary outcome was met but the glucose arm was terminated early.**
**** The primary outcome was met for combined macrovascular and microvascular events but not with macrovascular events alone.**

potassium ATP channels that may be affected by some of the drugs in the sulfonylurea class. The channels in the myocardium are known to be protective with improvement of coronary blood flow and limitation of myocardial damage during ischemia, a process known as ischemic preconditioning.[32] In the University Group Diabetes Project (UGDP), tolbutamide, a first-generation sulfonylurea, was associated with increased cardiovascular mortality.[33] First-generation sulfonylureas including glyburide were associated with an increased risk of cardiovascular death in a retrospective analysis by Simpson and colleagues.[34] In another observational study, patients taking sulfonylurea drugs during the first 48 hours after emergency angioplasty had an associated 24% increased rate of mortality.[35] In contrast, no increased risk of cardiovascular events was found with patients receiving glyburide or chlorpropamide in the UKPDS trial.[20] In spite of numerous trials, no consensus has been reached regarding the effects of sulfonylureas on cardiovascular disease. However, second-generation sulfonylureas are preferred due to their decreased risk of hypoglycemia.

On the other hand, metformin has been linked to a reduction in cardiovascular mortality. In a subset of obese patients in the UKPDS, metformin was associated with a 30% reduction in cardiovascular mortality.[21] This remained significant in the 10-year follow-up study.[24]

There has been some controversy regarding the cardiovascular benefits and risks in patients taking thiazolidinediones (TZD). In 2007, a meta-analysis by Nissen et al. published in the *New England Journal of Medicine* suggested that rosiglitazone was associated with an increased risk of MI and death from cardiovascular causes.[36] This article has since been criticized for using inadequate summary level data from trials that were small, included few adverse cardiovascular events, and were not originally intended to look at cardiovascular outcomes.[37] The results of the Nissen review triggered an unplanned interim analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes (RECORD) trial. During a 3.75-year period, there were no statistically significant differences between the rosiglitazone group and the control group regarding MI or death from cardiovascular causes.[38] In the completed RECORD trial, a hazard ratio of 0.99 was found for the primary outcome, suggesting that the addition of rosiglitazone to metformin and a sulfonylurea was not inferior to metformin and a sulfonylurea alone.[39]

Concern arose that pioglitazone also may have an increased risk of cardiovascular mortality. This was not seen in the PROspective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) trial. The PROactive trial evaluated more than 5000 patients with type 2 diabetes and a history of macrovascular disease. Patients received either placebo or pioglitazone, which was added to their current therapy. The primary outcome was time from randomization to occurrence of a new macrovascular event or death. A nonsignificant 10% reduction ($p = 0.095$) in the primary endpoint was reached with pioglitazone as compared to placebo. A significant 16% reduction ($p = 0.027$) in MI, stroke, and premature death also was noted in the pioglitazone group.[40]

Pioglitazone also has shown a favorable cardiovascular risk profile in the Carotid Intimal-Medial Thickness in Atherosclerosis using Pioglitazone (CHICAGO), the Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE), and multiple other trials.[41,42] There was no evidence of increased cardiovascular risk with either pioglitazone or rosiglitazone in the recent ACCORD or ADVANCE trials.[25,26] The American Heart Association (AHA) and American College of Cardiology Foundation (ACCF) released a scientific advisory stating that there is

insufficient evidence to determine the role of pioglitazone or rosiglitazone in CVD. They also noted that there was insufficient evidence to indicate that either pioglitazone or rosiglitazone should be utilized over the other.[43]

A recent retrospective meta-analysis looked at the risk of CVD and all-cause mortality between first- and second-generation sulfonylureas, metformin, rosiglitazone, and pioglitazone. First- and second-generation sulfonylureas were associated with a 24-61% increased risk of all-cause mortality ($p < 0.001$), and second-generation sulfonylureas were associated with an 18-30% increased risk of congestive heart failure in comparison to metformin ($p = 0.01$ and $p < 0.001$). This brings into question the use of not only first-generation sulfonylureas but also second-generation ones. Neither pioglitazone nor rosiglitazone was associated with an increased risk of an MI. Piogliatzone was associated with a 31-39% decreased risk of all-cause mortality in comparison to metformin ($p = 0.02$ to $p < 0.001$). Rosiglitazone had a higher risk of all-cause mortality (34-41%) compared to pioglitazone ($p = 0.14$ to $p = 0.01$).[44] These results suggest a benefit of pioglitazone over rosiglitazone. Further prospective studies are needed to confirm the associations seen in the meta-analysis before the findings can be instituted into practice.

## Role of Postprandial Hyperglycemia and Glycemic Variability

A1c has been the gold standard for glucose control in the previously mentioned large prospective studies. A1c is an average of fasting and postprandial blood glucose but does not take into account glycemic variability. Due to this, patients with vastly different blood glucose readings may end up with similar A1c values. It has been proposed that glycemic variability plays a large role in microvascular and macrovascular complications and should be taken into consideration when evaluating patients. Risk of retinopathy progression, despite the same A1c, differed between patients treated intensively and conventionally in the DCCT trial.[45] Glycemic variability has been proposed as the reason for this difference. In the ACCORD and VADT trials, patients experiencing a severe hypoglycemic event had a higher risk of cardiovascular mortality in the standard versus the intensive treatment arm.[28] Again, glycemic variability may have played a role in the increased mortality seen in the standard group.

Epidemiological studies have provided increasing evidence suggesting that postprandial hyperglycemia may be an independent risk factor for cardiovascular disease and mortality. In the Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe (DECODE) study, 25,000 patients were followed for seven years after a cardiovascular event. Two-hour postprandial hyperglycemia was found to have a higher correlation with increased mortality than fasting glucose.[46] Smaller studies including the Hoorn study, the Honolulu Heart Program, and the Chicago Heart Study also found that 1-2 hour post-meal hyperglycemia predicted mortality.[47-49]

One theory is that glycemic variability and postprandial glucose excursions lead to increased mitochondrial production of reactive oxygen species. Ceriello et al. noted that nitrotyrosine, a marker of oxidative stress, was increased at fasting and then further increased after meals in patients with type 2 diabetes but not in their non-diabetic counterparts.[50] Urinary 8-isoprostane prostaglandin-2 alpha (8-iso PGF 2 $\alpha$), another marker of oxidative stress, also has been associated with increased levels in patients with type 2 diabetes and was significantly correlated with mean average glucose excursions (MAGE) and mean postprandial incremental area under the curve (AUCpp).[51] These were both small trials and need to be repeated on a larger scale to determine their clinical significance.

Few interventional trials aimed at decreasing postprandial hyperglycemia and glycemic variability have been carried out. Future trials need to be completed to look at the influence of postprandial hyperglycemia and glycemic variability on diabetes complications.

## Future Studies

Tiered glucose and A1c goals may need to be established for patients with low versus high risk of cardiovascular disease. Future trials in patients with new onset type 2 diabetes without a history of cardiovascular disease need to be evaluated. In this trial, the use of other glycemic targets such as postprandial glucose and glycemic variability should be assessed. The use of medications with a low risk of hypoglycemia should be utilized, and optimal treatment of all other cardiovascular risk factors needs to be carried out.

Incretin therapies may have a decreased risk of hypoglycemia compared to some of the other diabetes therapies. Incretin medications were not utilized in any of the studies discussed previously. Exenatide (GLP-1 mimetic), liraglutide (GLP-1 agonist), sitagliptin (DDP 4 inhibitor), and saxagliptin (DDP 4 inhibitor) are currently available for clinical use in the United States. GLP-1 receptors have been found in cardiac myocytes and regions of the brain that regulate autonomic flow.[52] A report from open-label extensions of various exenatide trials suggests a benefit in cardiovascular risk factors, including a reduction in blood pressure (2.6 mmHg/1.9 mmHg), an increase in HDL-C (4.6 mg/dL), and a decrease in triglycerides (38.6 mg/dL).[52] It has been hypothesized that incretin medications would be beneficial in the reduction of macrovascular disease. This is based on their reduction in postprandial hyperglycemia, low risk of hypoglycemia, and the possibility of associated weight loss. To date, there have been no long-term trials looking at cardiovascular risk reduction with the use of incretin therapies.

***Table 5:*** Targets and Mean Levels Obtained in the Steno-2 Trial and Follow-up[10]

| Characteristic | Target | End of Intervention | | End of Follow-up | |
|---|---|---|---|---|---|
| | | Intensive | Conventional | Intensive | Conventional |
| A1c (%) | 6.5 | 7.9 | 9.0 | 7.7 | 8.0 |
| BP (mmHg) | 130/80 | 131/73 | 146/78 | 140/74 | 146/73 |
| Total-C (mg/dL) | 175 | 159 | 216 | 147 | 155 |
| TG (mg/dL) | 150 | 115 | 159 | 99 | 148 |
| LDL-C (mg/dL) | | 83 | 126 | 71 | 77 |
| HDL-C (mg/dL) | | 47 | 45 | 51 | 47 |

## Summary of Glycemic Control on Macrovascular Disease

The recent studies aimed at explaining the role of intensive glucose control in the reduction of cardiovascular risk have left physicians with more questions than answers. What these studies have answered is that one glucose target probably should not be used for all patients with diabetes. In sub-analyses of the ACCORD and VADT trials, patients without a previous cardiovascular event, a shorter duration of diabetes, and lower baseline A1c values had a statistically significant reduction in cardiovascular events and mortality with intensive glucose control.[28] This emphasizes the point of starting aggressive therapy early in the course of the disease in an effort to prevent complications. On the other hand, patients with a higher risk of cardiovascular disease, longer duration of diabetes, and difficulty in attaining glucose control should be treated with caution and may benefit from a slightly higher A1c.

The significance of hypoglycemia, specific medications, glycemic variability, and postprandial hyperglycemia on macrovascular outcomes is still ultimately unknown and requires further research in large randomized controlled trials.

## Multifactorial Risk Reduction

Despite the controversy of intensive glucose control in cardiovascular risk reduction, there is no question that a multifactorial approach is successful. The Steno-2 trial evaluated 160 patients with type 2 diabetes and persistent micro-albuminuria over 7.8 years and then observed these patients for an additional 5.5 years. All patients were placed on a blocker of the renin-angiotensin system due to micro-albuminuria and were on aspirin for primary prevention. Targets and mean levels obtained for blood pressure, cholesterol, and glucose are located in Table 5. Intensive therapy was associated with a 53% reduction in CVD at the end of the intervention period ($p = 0.007$).[53] Patients were then observed for an additional 5.5 years and ended up with similar A1c values between the two therapy groups. Despite this, 13.3 years after trial initiation, there was an even higher risk reduction in cardiovascular events (59%; $p < 0.001$) and a 20% absolute reduction ($p = 0.02$) in death from any cause with intensive versus conventional therapy.[54] Yet again, this supports the theory of metabolic memory and the legacy effect.

**Take Home Points:**

- Diabetes mellitus is associated with a two- to four-fold increased risk of cardiovascular disease, which is the leading cause of mortality in diabetes patients. Cardiovascular disease accounts for up to 70-80% of all deaths in people with diabetes.
- Multifactorial risk factor reduction is the most important therapy for prevention of macrovascular disease and is associated with a 59%. reduction in cardiovascular events.
- Patients without a previous cardiovascular event, a shorter duration of diabetes, and lower baseline A1c values had a statistically significant reduction in cardiovascular events and mortality with intensive glucose control in ACCORD and VADT.
- Early intensive treatment of hyperglycemia does not appear to reduce immediate cardiovascular risk but may have long-lasting effects that decrease the risk for macrovascular complications, the legacy effect.
- There is insufficient evidence regarding the cardiovascular risk profile of rosiglitazone and pioglitazone.
- Future studies are needed on the effects of hypoglycemia, postprandial hyperglycemia, glycemic variability, and incretin therapies on cardiovascular risk reduction.
- Different glucose targets should be used based on the patient's cardiovascular risk, duration of diabetes, and risk of hypoglycemia.

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## Physician CME Questions

20. What percentage of deaths in patients with diabetes are secondary to cardiovascular disease?
    A. 30-40%
    B. 40-50%
    C. 50-60%
    D. 70-80%

21. Which medication has proven cardiovascular benefit in patients with type 2 diabetes?
    A. glyburide
    B. metformin
    C. rosiglitazone
    D. glargine

22. Which trial was associated with an increase in mortality with intensive glucose control?
    A. ACCORD
    B. UKPDS
    C. ADVANCE
    D. DCCT
    E. VADT

23. Patients with a previous cardiovascular event, a shorter duration of diabetes, and lower baseline A1c values may have a reduction in cardiovascular events and mortality with intensive glucose control.
    A. true
    B. false

24. What is the etiology of cardiovascular events in the majority of patients with diabetes?
    A. total vessel occlusion
    B. atherosclerotic plaque rupture
    C. complication from percutaneous intervention
    D. cocaine abuse with subsequent vasoconstriction

25. Cardiovascular risk reduction with intensive glucose control was obtained in a higher percentage of patients with type 1 diabetes in comparison to patients with type 2 diabetes in the observational trials of DCCT/EDIC and UKPDS, respectively.
    A. true
    B. false

26. The multifactorial approach including cholesterol, blood pressure, and glucose therapy in the Steno-2 trial was associated with what percentage reduction in cardiovascular events?
    A. 10-20%
    B. 20-40%
    C. 50-60%
    D. 80-90%

## CME Answer Key

20. D; 21. B; 22. A; 23. A; 24. B; 25. A; 26. C

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By Louis Kuritzky, MD

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## BP response of atenolol vs HCTZ

**Source:** Beitelshees AL, et al. Comparison of office, ambulatory, and home blood pressure antihypertensive response to atenolol and hydrochlorthiazide. *J Clin Hypertens* 2010;12:14-21.

In untreated subjects with hypertension (HTN), findings on 24-hour ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBP) have been found to provide better indication of risk than office blood pressure (OBP). On-treatment BP measurement using the same techniques shows similar associations: ABPM is better than HBP, which is better than OBP for risk prediction. Since not all patients can be availed of ABPM, HBP monitoring has received increased advocacy.

HCTZ and atenolol (ATN) are two of the most commonly prescribed antihypertensive agents in the United States. Beitelshees et al performed a randomized controlled trial to assess the relative accuracy of OBP and HBP compared to the gold standard ABPM in subjects (n = 418) treated with HCTZ, atenolol, or the combination.

For both systolic and diastolic BP, correlation with ABPM was significantly better for HBP than OBP. For example, OBP overestimated treatment effects on SBP by 4.6 mm Hg compared with HBP. Recent HTN consensus groups have endorsed routine HBP monitoring; these data support the role of HBP monitoring as a better risk predictor than OBP. ■

## Ipratropium and CV events in COPD

**Source:** Ogale SS, et al. Cardiovascular events associated with ipratropium bromide in COPD. *Chest* 2010;137:13-19.

Bronchodilators (i.e., inhaled beta agonists and anticholinergics) are the foundation of symptomatic care for COPD. Metered-dose inhaler administration of ipratropium (IPR) is generally very well tolerated, and associated with few, if any, adverse symptoms. Nonetheless, there remains some conflict about the cardiovascular safety of anticholinergic bronchodilators in COPD. One meta-analysis suggested as much as a 53% increased relative risk for MI in COPD patients treated with IPR; in contrast, a large randomized prospective trial with tiotropium (n = 6000, approximately) did not find any signal for increased cardiovascular events.

Ogale et al performed a cohort study comprised of newly diagnosed COPD patients (n = 82,717) attending an Illinois VA hospital.

Risk for a cardiovascular event was 29% higher in COPD patients treated with IPR than comparators. Risk was time-related: Those with at least a 6-month interval since last exposure to an anticholinergic were not at greater risk. The mechanism by which anticholinergics might increase cardiovascular risk is not clear, although a dose-response relationship between IPR and supraventricular tachyarrhythmia incidence noted in the Lung Health Study intimates a possible connection. ■

## Kidney function, proteinuria, and adverse outcomes

**Source:** Hemmelgarn BR, et al. Relations between kidney function, proteinuria, and adverse outcomes. *JAMA* 2010;303:423-429.

Staging of chronic kidney disease (CKD) is based primarily upon estimated GFR. Proteinuria (PRO) is a strong marker for kidney disease, yet its severity is not included in current risk stratification schemes, which are instead driven by GFR. Indeed, the majority (75%) of proteinuric patients do not have a GFR < 60 mg/min. Intuitively, since either PRO or stage of CKD predicts risk, the combination of the two might be an even better risk predictor.

To study the relationship of CKD, PRO, or the combination with outcomes, data from 920,985 Canadian adults was analyzed. Persons with end-stage renal disease at study inception were excluded.

Over 35 months of follow-up, for each decrement in GFR, all-cause mortality, MI, and end-stage renal disease increased. Within each quartile of GFR, progressively increasing levels of proteinuria (normal, mild, heavy) were associated with increased risk. Persons with the very lowest GFR (i.e., most advanced kidney disease), however, experienced less relative impact per degree of proteinuria; in other words, adverse outcomes are more compounded by proteinuria in CKD 2-4 than CKD 5.

The recent adoption of a standardized staging system for CKD is a major step forward. These data suggest that future stratification methods would benefit from inclusion of proteinuria as well as GFR. ■

## Remission of diabetes with bariatric surgery

**Source:** Wilson JB, Pories WJ. Durable remission of diabetes after bariatric surgery: What is the underlying pathway? *Insulin* 2010;5:46-55.

THE BURGEONING POPULATION OF individuals with type 2 diabetes (DM2) corresponds to a parallel increase in obesity. Although bariatric surgery produces prompt and sustainable weight loss, the post-surgical rapidity with which derangements of diabetes resolve defies explanation by weight loss alone.

Bariatric surgical procedures that eliminate food contact with the duodenum and jejunum — as opposed to gastric banding type procedures — produce not only substantial weight loss, but also provide remission of DM2 within days. Indeed, as many as 80% of DM2 patients leave the hospital with no diabetes medications, and more than 75% remain DM2-free 5 years later. Similar reversion to normal glucose handling has also been seen in IGT patients who have bypass surgery.

Post-surgical benefits of bariatric surgery include resumption of normal menstrual function, BP and lipid improvements, and reductions in diabetes-related mortality. Studies of gastric banding conclude that weight loss is responsible for these favorable outcomes; in contrast, bariatric bypass surgery, although enjoying benefits attributable to weight loss, has other operant mechanisms: One report of intestinal bypass in lean DM2 individuals found resolution of diabetes without weight loss.

The GI tract has been increasingly recognized as a critical player in glucose dysregulation, as evidenced by evolution of the incretin mimetics and DPP-4 inhibitors. Resolution of dysglycemia within a few days — prior to meaningful weight loss — is characteristic of bariatric bypass surgery. ■

## Inhaled corticosteroids and COPD exacerbations

**Source:** Agarwal R, et al. Inhaled corticosteroids vs placebo for preventing COPD exacerbations: A systematic review and metaregression of randomized controlled trials. *Chest* 2010; 137:318-325.

ACUTE EXACERBATIONS OF COPD (AECOPD) are costly to patients. Not only is the symptomatic deterioration and commonplace requirement for hospitalization burdensome, but an AECOPD is typically followed by loss of pulmonary function that does not return. Additionally, mortality from hospitalized AE-COPD has been reported to be as high as 10%.

We have no known disease-modifying pharmacotherapy for COPD. Although symptom improvement is considerable from bronchodilators and inhaled corticosteroids (ICS), they do not change disease progression. Short of that outcome, reduction in AE-COPD is a worthy goal to seek.

Agarwal et al reviewed data from 11 placebo-controlled COPD trials (n = 8164) employing ICS to examine the impact upon AE-COPD. Overall, ICS use was associated with an 18% relative risk reduction in AE-COPD; this beneficial effect was driven primarily by persons with an FEV1 < 50%.

Recent meta-analyses have shown an increased risk of pneumonia in COPD patients receiving ICS. Because the risk reduction for AE-COPD is modest, careful consideration to the risk-benefit balance of ICS use is appropriate. ■

## Non-alcoholic fatty liver disease in Japanese patients

**Source:** Hamaguchi E, et al. Histological course of nonalcoholic fatty liver disease in Japanese patients. Tight glycemic control, rather than weight reduction, ameliorates liver fibrosis. *Diabetes Care* 2010;33:284-286.

IN THE UNITED STATES, DIABETES AND metabolic syndrome are the disorders most commonly associated with nonalcoholic fatty liver diseases (NAFLD). Because obesity, dyslipidemia, hypertension, and insulin resistance are typical operative components of these disorders, it is difficult to make a clear attribution about which is the primary culprit leading to NAFLD.

Japanese subjects do not demonstrate the same degree of obesity as Americans. Study of NAFLD in this population might provide insight about the primary drivers of pathology.

Serial liver biopsies on two occasions were obtained from 39 Japanese NAFLD patients over a mean follow-up of 2.4 years. During this interval, NAFLD improved in 30.7%, worsened in 28.2%, and was unchanged in 41%.

Improvement in glycemic control, as measured by A1C, was the best predictor of NAFLD improvement. Transforming growth factor-beta and plasminogen activator inhibitor type 1 are known regulators of hepatic fibrosis, both of which are stimulated by high glucose levels. ■

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PHARMACOLOGY WATCH

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# Thiazolidinediones and Risk of Heart Failure

***In this issue:*** FDA is reviewing safety of TZDs; SSRI use with tamoxifen; Metformin smells like fish; FDA Actions.

## FDA reviews TZD safety

Thiazolidinediones (TZDs) have been under intense scrutiny in recent years after rosiglitazone (Avandia®) was linked to increased cardiovascular morbidity and mortality in several studies. In recent weeks, *The New York Times* has reported that some FDA staffers are recommending that rosiglitazone be removed from the market. According to the story in the *Times*, a "confidential government report" states that about 500 heart attacks and 300 cases of heart failure per month could be averted if patients were switched from rosiglitazone to pioglitazone (Actos®). Congress has even gotten involved, specifically the Senate's Committee on Finance, which in January issued a 350-page report on rosiglitazone, focusing on GlaxoSmithKline's handling of evidence of possible cardiac risks associated with use of the drug. Now the American Heart Association and the American College of Cardiology have weighed in on the issue suggesting there is insufficient evidence to support the use of pioglitazone over rosiglitazone and that both drugs increase the risk for heart failure and should not be initiated in patients with class III/IV heart failure. They further state that the drugs should not be used with an expectation of benefit with respect to ischemic heart disease events (*Circulation*, published on-line Feb. 23, 2010). Meanwhile, the FDA web site reports that the Agency is reviewing data on rosiglitazone and is planning a public meeting in July 2010 to present all known heart-related safety data on the drug and provide an updated assessment of the risks and benefits of rosiglitazone and the treatment of type 2 diabetes. ■

## SSRI use with tamoxifen

The SSRI paroxetine (Paxil®) reduces the effect of tamoxifen in women with breast cancer leading to higher breast cancer mortality according to a new study in the *British Medical Journal*. Concern about SSRIs interfering with the metabolism of tamoxifen was raised last June at the American Society of Clinical Oncology meeting. Tamoxifen is converted from its prodrug to the active metabolite via the cytochrome P450 pathway, specifically CYP2D6. Paroxetine is an exceptionally strong inhibitor of CYP2D6, the strongest inhibitor of all the SSRIs. In the study, Canadian researchers looked at more than 2400 women from Ontario treated with tamoxifen for breast cancer along with a single SSRI. After adjustment for confounders, absolute increases of 25%, 50%, and 75% in the proportion of time on tamoxifen with overlapping use of paroxetine were associated with 24%, 54%, and 91% increases in the risk

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of death from breast cancer, respectively ($P < 0.05$, for each comparison). No such risk was seen with any other antidepressant. The authors conclude that paroxetine use during tamoxifen treatments is associated with an increased risk of death from breast cancer, supporting the hypothesis that paroxetine can reduce or abolish the benefit of tamoxifen in women with breast cancer (*BMJ* 2010;340:c693). The study is important because up to one-quarter of women diagnosed with breast cancer experience a depressive disorder, and antidepressants are commonly used during tamoxifen treatment for not only depression, but also for treatment of hot flashes and other symptoms. It is evident that paroxetine should never be prescribed to women taking tamoxifen for treatment of breast cancer and that preference should be given to antidepressants that show little or no inhibition of CYP2D6. Among the SSRIs, the strongest inhibitors of CYP2D6 besides paroxetine are fluoxetine (Prozac®), duloxetine (Cymbalta®), and to a lesser extent sertraline (Zoloft®). Among non-SSRI antidepressants, bupropion (Wellbutrin®) also is a strong CYP2D6 inhibitor. Drugs that are not inhibitors of the enzyme include citalopram (Celexa®) and venlafaxine (Effexor®). ■

## Generic metformin smells fishy?

If your patients tell you their pills smell like fish, they may be taking generic metformin. A letter to the *Annals of Internal Medicine* describes two patients who stopped taking generic metformin because of a fishy taste that caused nausea. The fishy smell is a property of metformin and is well known to pharmacists. Apparently the film-coated extended-release formulations have less smell and may be better tolerated (*Ann Intern Med* 2010;152:267-268). ■

## FDA actions

A new FDA warning states that **long-acting beta agonists** (LABAs) should never be used alone in the treatment of asthma in children or adults. The LABAs salmeterol (Serevent®) and formoterol (Foradil®) have been associated with severe worsening of symptoms when used without a controller medication such as an inhaled corticosteroid. Both products will be required to include warnings on the product label that states:

- Use of LABAs is contraindicated without the use of an asthma controller medication;
- LABAs should only be used long term in patients whose asthma cannot be adequately controlled on asthma controller medications;
- LABAs should be used for the shortest duration of time required to achieve control, and should be discontinued once asthma control is achieved;
- Pediatric and adolescent patients who require an LABA in addition to an inhaled corticosteroid should use a combination product containing both an inhaled steroid and a LABA to ensure compliance with both medications.

The FDA has approved **rosuvastatin (Crestor®)** for primary prevention in patients without elevated LDL-cholesterol but who have an elevated C-reactive protein (2 mg/L or higher) and at least one additional cardiovascular risk factors such as low HDL, hypertension, or family history of premature heart disease. The approval was based on the JUPITER trial, which showed a 44% reduced relative risk of cardiovascular events in patients with normal LDL cholesterol but elevated CRP.

The FDA has approved a new **pneumococcal vaccine** for infants and children. Wyeth Pharmaceuticals' **Prevnar 13™** is a 13-valent conjugate vaccine that will replace the currently available 7-valent Prevnar®. It is approved for the prevention of invasive disease caused by 13 different serotypes of *S. pneumoniae*.

The FDA has approved the **monoclonal antibody rituximab (Rituxan®)** to treat certain patients with chronic lymphocytic leukemia (CLL). Rituximab is approved for CLL patients who are starting chemotherapy for the first time and also for those who have not responded to other CLL therapies. It is administered with fludarabine and cyclophosphamide for the treatment of CLL. Rituximab is manufactured by Genentech.

The FDA is initiating a risk-management program for **erythropoiesis-stimulating agents** (ESAs) for the treatment of chemotherapy-related anemia. The drugs, which include epoetin alfa (Procrit®, Epogen®) and darbepoetin alfa (Aranesp®), have been associated with accelerated tumor growth and higher mortality rates in some cancer patients. The Risk Evaluation and Medication Strategy (REMS) requires that patients receive a medication guide on safety issues associated with the drugs and requires training and certification of health care professionals who administer chemotherapy to patients with cancer and counseling of patient regarding the risks of the drugs. The REMS does not currently apply to patients being treated with an ESA for anemia due to other conditions, specifically renal failure. ■