Management of Patients with Prediabetes: Is it More Than Just Watchful Waiting?

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**Objective:**
At the conclusion of this knowledge-based activity, the pharmacist will be able to:
1) Define prediabetes and identify risks associated with prediabetes.
2) Review current treatment guidelines from the American Diabetes Association (ADA) for patients with prediabetes.
3) Evaluate other aspects of ADA Diabetes Standards of Care that can apply to patients with prediabetes.
4) Design therapeutic regimens for patients with prediabetes.

**Abstract**
Type 2 diabetes is a growing health problem in the United States with approximately 1.7 million newly diagnosed cases each year. Diabetes is the 7th leading cause of death in the U.S., and is associated with a myriad of complications including hypertension, hyperlipidemia, obesity, microvascular complications, and heart disease. In order to reduce the incidence of diabetes, it is important to recognize those at risk and intervene quickly. This article aims to identify patients with prediabetes and recommend appropriate evidence-based therapies to reduce the risk of patients developing overt diabetes or other complications. The following recommendations are based on the ADA 2015 Diabetes Standards of Care, the 2013 American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines, 2014 AHA/ American Stroke Association (ASA) guidelines, and evidence from clinical trials. The ADA guidelines recommend that all patients with prediabetes receive counseling on lifestyle modifications including diet, exercise, and smoking cessation. When clinically indicated to further reduce risk, pharmacotherapy interventions should be considered, including metformin, statins, aspirin, angiotensin-converting enzyme (ACE) inhibitors, and vaccinations.

**Keywords:** prediabetes; type 2 diabetes; hypertension; hyperlipidemia; obesity; statins; ACE-inhibitors

**Introduction**
Prediabetes is defined as a state of altered glucose metabolism, resulting in higher than normal blood glucose levels which are below the threshold for a diagnosis of diabetes. According to the National Diabetes Statistics Report of 2014, approximately 86 million people in the U.S. aged 20 years or older suffer from prediabetes. This estimate is based on data collected from 2009 to 2012 by the National Health and Nutrition Examination Survey (NHANES). Individuals surveyed in the NHANES were classified as having prediabetes by having either an elevated fasting plasma glucose (FPG) 100 to 125 mg/dL or a hemoglobin A1c 5.7 to 6.4%. This standard is consistent with diagnostic criteria used by the ADA. This intermediate stage of prediabetes often precedes the onset of type 2 diabetes in at-risk patients. Risk factors for prediabetes are comparable to those for diabetes, including physical inactivity, family history of diabetes, obesity, cardiovascular disease, dyslipidemia, and past history of gestational diabetes (Table 1). Despite these known risk factors, findings from the 2012 NHANES showed the prevalence of prediabetes increased in the U.S. from 2010 to 2012, and the number of individuals classified as having prediabetes aged 20 years or older escalated from 79 million to 86 million. The increasing prevalence of prediabetes is likely linked to the current obesity epidemic in the U.S., with the highest incidence of prediabetes found in surveyed individuals that were either overweight or obese.

While many patients remain in the prediabetes stage for several years, evidence shows within five years 15-30% of patients with untreated prediabetes will develop type 2 diabetes. According to an expert ADA panel, up to 70% of untreated patients with prediabetes will eventually develop type 2 diabetes. This strong correlation of progression makes early diagnosis and treatment of prediabetes crucial in improving patient outcomes and preventing...
or delaying overt diabetes and further preventing microvascular and macrovascular complications. Microvascular complications include patient burdens such as retinopathy, nephropathy and neuropathy, whereas macrovascular complications include ischemic heart disease, peripheral vascular disease and cerebrovascular disease.

**Screening/Diagnosis**

The first step to prevent the onset of type 2 diabetes is to identify those at risk. The ADA recommends screening asymptomatic patients of all ages who are overweight or obese (body mass index (BMI) ≥ 25 kg/m²), and who have at least one additional risk factor for developing diabetes.\(^1\)\(^,\)\(^2\)\(^,\)\(^3\)^\(^,\)\(^4\) For patients with a BMI ≥ 25 kg/m² without additional risk factors, the ADA recommends screening for diabetes starting at 45 years of age.\(^1\)\(^,\)\(^3\)\(^,\)\(^4\)

Traditional laboratory tests for diagnosis of type 2 diabetes can also be used to screen for prediabetes. Impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and hemoglobin A1c can all be used to screen for prediabetes.\(^1\)\(^,\)\(^3\)\(^,\)\(^4\) While all of these laboratory tests measure blood glucose concentrations, each is performed differently and have discrete values that correspond to either a diagnosis of prediabetes or diabetes (Table 2).\(^1\)\(^,\)\(^4\) IFG measures a patient’s blood glucose concentration when he/she has not eaten in the past eight to twelve hours which determines if their fasting glucose levels are abnormal. IGT utilizes an oral glucose tolerance test (OGTT), which measures the blood glucose concentration two hours after ingestion of 75 grams of glucose. OGTT determines if the patient has an abnormal tolerance to a glucose load. Finally, a hemoglobin A1c measures a patient’s average blood glucose concentration over the past two to three months. In patients with prediabetes, these results are higher than normal but not quite high enough to classify patients as having diabetes.\(^1\)\(^,\)\(^4\) For an accurate diagnosis of prediabetes or diabetes, it is recommended that any positive test be repeated for confirmation.\(^4\) For example, an initial hemoglobin A1c of 5.9% along with the repeat value yielding a hemoglobin A1c of 6.2% supports a diagnosis of prediabetes. Similarly, a FPG of 115 mg/dL plus an OGTT result of 160 mg/dL also confirms prediabetes. However, if two different laboratory values yield conflicting results, the positive test must be repeated for confirmation. The ADA recommends all of these tests be performed via venipuncture using clinical laboratory equipment, as point-of-care testing instruments do not have the accuracy or precision necessary to diagnose prediabetes or diabetes.\(^4\)

According to the Centers for Disease Control (CDC), nine out of ten patients with prediabetes are unaware of their condition or its associated risks.\(^2\) By conducting medication profile reviews and recognizing risk factors such as obesity, hypertension, and hyperlipidemia, pharmacists and pharmacy technicians play a key role in determining patients at risk for prediabetes.

**Lifestyle Modifications and Metformin**

Delaying the progression from prediabetes to diabetes requires early detection and intervention. The Diabetes Prevention Program (DPP) Research Group conducted a large, randomized controlled trial consisting of 3,234 patients without diabetes but with elevated blood glucose concentrations. Patients were randomized to one of the following groups: standard lifestyle intervention plus metformin 850 mg twice daily; standard lifestyle intervention plus placebo; or intensive lifestyle intervention. Intensive lifestyle intervention included weight loss of at least 7% of initial body weight through a healthy diet low in calories and fat (< 25% of calories from fat) as well as at least 150 minutes of moderate intensity exercise per week.\(^7\) In the first 24 weeks following enrollment, participants individually met with case managers to discuss changes assisting the patients in reaching their exercise and weight loss goals. Meetings were flexible due to their individualized nature, but all patients followed a set curriculum of 16 lessons focusing specifically on diet, exercise, and behavior. After the initial 24 weeks, continued support was provided in the form of individual monthly and group sessions led by the case managers.\(^7\)

Standard lifestyle intervention, on the other hand, involved much less individual attention for participants and less stringent goals. Patients were instructed to follow the Food Guide Pyramid as well as a curriculum similar to a National Cholesterol Education Program for their diet and exercise education. These instructions, however, consisted mostly of written information. Standard intervention participants received an individual consultation once a year, lasting 30 minutes. Discussions focused on the general goal of a “healthy lifestyle,” instead of specific goals for weight loss, dieting, and exercise.\(^7\)

Eligibility for inclusion in the DPP study involved subjects being at least 25 years of age, a BMI ≥ 24 kg/m², a FPG of 95 to 125 mg/dL and an OGTT of 140 to 199 mg/dL. Participants were excluded from the study if they were taking glucose altering medications or had illnesses that could impact their ability to participate. The mean age of study participants was 51 years, and the mean BMI was 34 kg/m², which is classified as obese. Women made up 68% of the participants, and 45% of participants were members of minority groups including African American, Hispanic, Native American, and Asian.\(^7\)

The results of the DPP study proved that intensive
lifestyle modifications and treatment with metformin were each effective means of preventing the progression to type 2 diabetes in at-risk patients. Intensive lifestyle modifications provided the greatest reduction (58% reduced incidence) in progression to diabetes with one diabetes case prevented for every seven people treated over a period of three years.\textsuperscript{7} Additionally, in obese patients with a FPG 110-125 mg/dl, metformin delayed the onset of diabetes.\textsuperscript{7} In study participants with a BMI $\geq$ 35 kg/m\textsuperscript{2}, standard lifestyle modifications plus metformin therapy was shown to be as effective as intensive lifestyle modifications in delaying diabetes onset.\textsuperscript{1,4,7} Metformin, however, was not significantly superior to placebo in patients $> 60$ years of age. Therefore metformin may not be beneficial for treatment of prediabetes for patients in this age group.\textsuperscript{4,7}

The results from the DPP study have influenced the prediabetes treatment recommendations in the ADA guidelines. In patients at risk for developing type 2 diabetes, the ADA recommends lifestyle modifications consisting of 5-10% weight loss of total body weight, 30 minutes of moderate-intensity exercise daily, and smoking cessation.\textsuperscript{3,4} The ADA also recommends use of metformin in patients at highest risk for progression to diabetes who were shown to benefit from its use in the DPP study (Table 3).\textsuperscript{1,4,7,9} Patients treated with metformin should be started on a low dose initially and titrated upward to reduce the risk of gastrointestinal side effects; they should also be counseled to take metformin with food for the same reason. In the DPP study, participants were initially started on metformin 850 mg once daily and then increased to twice daily after one month to minimize gastrointestinal discomfort.\textsuperscript{7} Patients also had the option of titrating the dose even more slowly by starting out on metformin 425 mg (one-half of the 850 mg tablet) once daily.\textsuperscript{7}

The Finnish Diabetes Prevention Study also demonstrated the positive effect of lifestyle changes in patients at risk for diabetes. In this study, 522 patients 45 to 65 years of age with a BMI $\geq$ 25 kg/m\textsuperscript{2}, an IGT (FPG < 140 mg/dL), and an OGTT result of 140-200 mg/dL were randomized to either control or the intervention group.\textsuperscript{8} The intervention included patient-specific counseling on diet, exercise, and weight loss.\textsuperscript{8} Specifically, diet changes included decreasing consumption of total and saturated fat as well as increasing dietary fiber.\textsuperscript{8} At the end of 2 years, the intervention group had lost significantly more weight than the control; 3.5±5.5 kg versus 0.8±4.4 kg, respectively ( $p<0.001$).\textsuperscript{8} After 4 years, the intervention group had a lower combined incidence of diabetes (11%; 95% CI 6-15%) than the control group (23%; 95% CI 17-29%).\textsuperscript{8} Lifestyle changes ultimately resulted in a 58% decrease in the intervention group’s risk of developing diabetes (HR 0.4, 95% CI 0.3-0.7; $p<0.001$).\textsuperscript{8}

**Thiazolidinediones and Alpha glucosidase Inhibitors**

While the ADA does not recommend thiazolidinediones (TZDs) or alpha glucosidase inhibitors, clinical trial data suggests these medications may have utility in prediabetes. Evidence from the “Study to Prevent Non-Insulin Dependent Diabetes Mellitus” (STOP-NIDDM) trial proposes that acarbose therapy may be beneficial in the treatment of prediabetes. In STOP-NIDDM, patients with a BMI of 25-40 kg/m\textsuperscript{2} and age 40-70 years with IGT (2 hour plasma glucose of 140-200 mg/dL after a 75 g glucose load) and IFG (FPG 101-139 mg/dL) were randomly assigned to receive either placebo or acarbose 100 mg three times daily. At the end of the study, significantly more patients in the placebo group developed diabetes compared to the acarbose group (HR 0.75, 95% CI 0.63-0.90; $p=0.0015$).\textsuperscript{9} Over a period of 3.3 years, acarbose was determined to reduce the risk of developing diabetes by 25%.\textsuperscript{9} Acarbose therapy, however, was associated with gastrointestinal side effects which directly resulted in 19% of patients in the acarbose group discontinuing the study early.\textsuperscript{9} Thus, acarbose may not be appropriate for patients with prediabetes who also have a history of gastrointestinal upset or conditions such as inflammatory bowel disease.

Another study looked at the use of pioglitazone in patients at risk for developing diabetes. The “Pioglitazone for Diabetes Prevention in Impaired Glucose Tolerance” study randomized 602 patients with IGT to receive either pioglitazone daily (titrated up to 45 mg) or placebo. Patients were followed for a median duration of three years.\textsuperscript{10} Yearly incidence rates of progression to diabetes were 2.1% in the pioglitazone group compared to 7.6% in the placebo group (HR: 0.28, 95% CI 0.16-0.49; $p<0.001$).\textsuperscript{10} Overall, pioglitazone was found to decrease the risk of progression to diabetes by 72% but did result in significantly more weight gain compared to placebo (3.9 kg vs. 0.77 kg, respectively; $p<0.001$) and edema (12.9% vs. 6.4%, $p=0.007$).\textsuperscript{10} Pioglitazone is not be recommended for the treatment of prediabetes in patients who have heart failure due to risk of these side effects.

In addition to recommending lifestyle interventions and potentially other pharmacologic therapies, patients with prediabetes should have their A1c tested at least once yearly to assess treatment efficacy.\textsuperscript{1,4} Furthermore, just as recommended for patients with diabetes in the ADA Diabetes Standards of Care, counseling on exercise, nutrition, and smoking cessation should be provided regularly to patients with
prediabetes to reinforce compliance with therapy. Pharmacists are in a great position to provide this counseling, especially in community settings where they have the potential for fairly regular interactions with patients. Pharmacy technicians can also help by providing patients with regular motivational support and encouragement toward positive lifestyle changes.

**Statins**

The ADA Standards of Care provide specific recommendations for managing patients with diabetes to reduce their risk of cardiovascular morbidity and mortality. However, there are no specific recommendations for patients with prediabetes regarding treatment options aimed at reducing cardiovascular events. The following is a discussion pertaining to literature which focuses on statin therapy to reduce atherosclerotic disease.

As diabetes is an independent risk factor for developing atherosclerotic cardiovascular disease (ASCVD), patients with prediabetes should have their 10-year ASCVD risk calculated in order to assess their need for additional therapy. A detailed patient history and recent laboratory measurements are needed to assess risk. Pertinent data includes blood pressure, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol concentrations. It is also necessary to gather information on smoking status, age, race, sex and use of antihypertensive therapy. The ACC/AHA Cardiovascular Risk Guidelines recommend assessment of these ASCVD risk factors every four to six years in all adults aged 20 to 79 years old without clinical ASCVD. Clinical ASCVD is defined as acute coronary syndromes, history of myocardial infarction (MI), stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral arterial disease presumed to be of atherosclerotic origin.

The overall goal of the 2013 AHA/ACC guidelines is matching the level of ASCVD risk to the intensity of statin treatment as opposed to the former guideline recommendation of targeting therapy to specific LDL concentrations. For patients with diabetes and a calculated 10-year risk score of < 7.5%, the 2013 AHA/ACC guidelines recommend primary prevention with a moderate intensity statin given once daily such as atorvastatin 10 mg, rosuvastatin 10 mg or simvastatin 20-40 mg. In patients with diabetes and a risk score of 7.5% or higher, a high intensity statin is warranted, whereas in patients without diabetes with this 10-year ASCVD risk, a moderate to high-intensity statin is recommended. High intensity statin treatment options include atorvastatin 40-80 mg or rosuvastatin 20-40 mg given once daily. For those with a previous ASCVD history, the ACC/AHA guidelines recommend secondary prevention with high-intensity statin therapy (Table 3). Evidence shows that ASCVD events are decreased using the highest tolerated statin doses and with each 39 mg/dL decrease in LDL cholesterol, this decreases ASCVD risk by approximately 20%. There are some data which link statin use to the increased risk of developing type 2 diabetes. Because our goal in treating patients with prediabetes is ultimately to prevent their progression to diabetes, it is important to discuss how the use of statins in this patient population has been controversial. One of the studies that brought the use of statins into question was the “Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin” (JUPITER) study. The JUPITER study was a randomized, double-blinded, placebo-controlled assessment of rosuvastatin 20 mg for primary prevention of cardiovascular events including MI, stroke, revascularization, unstable angina requiring hospitalization, and death related to cardiovascular causes. The study population was approximately 17,800 participants with LDL values < 130 mg/dL, high-sensitivity C-reactive protein (CRP) levels ≥ 2.0 mg/L, and no previous history of diabetes or cardiovascular disease. Minorities were also well represented with 6,801 women and 4,485 nonwhites included in the study. Results of the JUPITER study found while patients treated with rosuvastatin did have a significant reduction in cardiovascular events (45% reduction in whites and 37% reduction in nonwhites), the patients also had an increased incidence for developing type 2 diabetes. There were 270 new cases of diabetes reported in the treatment group versus 216 in the control group. It may seem that the results of the JUPITER trial prove that previously healthy individuals are at an increased risk of developing diabetes with statin use, which is a significant concern for patients with prediabetes. However, it is important to acknowledge pertinent confounding variables. Approximately 41% of participants had risk factors for diabetes, including impaired fasting glucose, a BMI > 30 kg/m², or a hemoglobin A1c > 6%. Additionally, 16% of patients reported using tobacco and 11.5% had family history of cardiovascular disease, increasing their risk for a cardiovascular event. It is possible that without intervention, many of these patients may have progressed to type 2 diabetes whether or not statins were used. This conclusion is further supported by the fact that 216 patients in the control group also developed diabetes. According to a recent meta-analysis, while statin use is associated with a significantly increased risk of new-onset diabetes, only one in five new cases are actually a direct result of statin therapy. It is the belief of the authors that the cardiovascular benefits of statin use in those with
prediabetes outweigh the potential risk of progression to type 2 diabetes. Furthermore, the JUPITER study found in those with risk factors for diabetes a total of 134 cardiovascular events, including death, were prevented for every 54 new cases of diabetes.\textsuperscript{13,14}

As with all other therapies, it is important for clinicians to weigh the potential risks and benefits of statin use for each individual patient and use evidence-based medicine to guide decision-making. When statin therapy is deemed appropriate for patients with prediabetes, pharmacy staff can play a critical role in optimizing therapy and preventing adverse events. Pharmacists and pharmacy technicians should be aware of the most common side effects with statins, which are muscle-related symptoms. If a patient is experiencing myalgia on a statin, he/she should be encouraged to contact the prescribing healthcare professional so that the patient can be further evaluated. The prescriber may opt to monitor a creatinine kinase (CK) concentration and a urinalysis to assess for rhabdomyolysis. If the benefit is outweighed by the risk of continued statin-induced myalgia, lower doses, every other day dosing, once weekly dosing, or alternate statins that are more lipophilic are some alternative dosing options. However, every other day and once weekly dosing strategies have not been studied to assess cardiovascular outcomes.\textsuperscript{16}

**Aspirin**

The ADA 2015 Standards of Care also emphasize annual cardiovascular disease risk assessment in patients with diabetes. The risk estimation calculates the 10-year risk of heart attack or stroke and evaluates the need for low dose aspirin therapy (Table 3).\textsuperscript{3,4} Per the 2014 AHA/ASA guideline for primary prevention of stroke, fasting hyperglycemia is associated with an increased risk of stroke.\textsuperscript{17} A study conducted for 31 years in 43,933 men with neither baseline cardiovascular disease nor diabetes recorded 595 strokes. In patients with a FPG 80-109 mg/dL, age-adjusted event rates for stroke demonstrated 8.2 cases per 10,000 person years. Age-adjusted event rates for patients with a FPG 110-125 mg/dL, had 9.6 strokes per 10,000 person-years. For patients with undiagnosed diabetes (FPG >126 mg/dL), the stroke rate was 12.4 cases per 10,000 person-years.\textsuperscript{17,18}

As evidenced in the aforementioned trial, patients with diabetes and prediabetes are at a higher risk of stroke and could benefit from a cardiovascular risk assessment to determine the need for aspirin therapy. It is important to note that there are multiple calculators that could potentially be used to conduct this assessment. While the ADA guideline does not specifically recommend any particular one, the Pooled Cohort Equation developed for the 2013 ACC/AHA lipid management guideline is recommended by the 2014 AHA/ASA guidelines for primary stroke prevention.\textsuperscript{17} Clinicians should use their own clinical judgment and compare results from various tools and estimators when making this decision. If the calculation results in a 10-year risk of >10% the ADA guideline recommends initiating aspirin 75-162 mg daily for primary prevention once their bleeding risk has been identified as acceptable.\textsuperscript{3,4} Additionally, all patients with a history of CVD should receive a low dose aspirin for secondary prevention.\textsuperscript{4}

Patients started on an aspirin regimen should be educated on the signs and symptoms of bleeding including abdominal pain, blood in urine or stool or unusual bruising. Additionally, pharmacists should recognize patients with contraindications to aspirin therapy such as those with known hypersensitivity or severe hepatic impairment and recommend against the use of aspirin in these patients. When aspirin therapy is not deemed appropriate, pharmacists should focus on counseling to reduce modifiable cardiovascular risk factors such as smoking cessation, weight loss, and exercise.\textsuperscript{49}

**ACE Inhibitors and ARBs**

Another aspect discussed in the ADA Standards of Care is the use of angiotensin-converting enzyme (ACE)-inhibitors or angiotensin-receptor blockers (ARBs) to manage blood pressure and/or albuminuria (defined as urine albumin-to-creatinine ratio \(\geq 30\) mg/g).\textsuperscript{4} Utility of ACE-inhibitors in prediabetes has been demonstrated in several landmark trials including the “Heart Outcomes Prevention Evaluation” (HOPE) trial.\textsuperscript{3,4} The HOPE trial was a double-blinded, randomized trial which enrolled 9,541 patients with and without diabetes. The primary outcome of the study was a combined endpoint of MI, stroke, or death from cardiovascular causes. Patients in the study were randomized to receive either ramipril or placebo once daily. The patients included in the study either did not have hypertension or were already adequately controlled on medications, with a mean blood pressure of 139/79 mmHg in both groups.\textsuperscript{19} For reference, the goal blood pressure for patients with diabetes and hypertension according to the ADA Standards of Care is <140/90 mmHg.\textsuperscript{5,4} According to results from the HOPE trial patients at high risk of cardiovascular disease can reduce their morbidity and mortality with the use of ACE inhibitors.\textsuperscript{19} The ramipril group compared to placebo also had a reduced incidence of new-onset diabetes (102 patients versus 155 patients, respectively) and diabetes-related complications (299 patients versus 354 patients, respectively).\textsuperscript{19} Diabetes related complications analyzed in the HOPE trial included diabetic nephropathy (defined as daily urinary excretion of at least 300 mg of albumin or 500 mg
of protein), renal dialysis, and diabetic retinopathy requiring laser therapy. Therefore, the HOPE trial showed that ramipril reduced both microvascular and macrovascular complications.

Another study entitled “ACE inhibitor-based versus diuretic-based antihypertensive primary treatment in patients with pre-diabetes” (ADA) assessed similar outcomes as in the HOPE trial, specifically in patients with prediabetes. In this study, 2,011 patients received either ramipril or a thiazide diuretic-based therapy for a median duration of 3 years. The primary endpoint of ADA was the first appearance of type 2 diabetes, defined as a FPG ≥ 126 mg/dL. The ramipril group had a significantly lower incidence of diabetes after 3 years compared to the thiazide diuretic (24.3% versus 29.0%, respectively). The odds ratio of 0.83 in ADA favors the use of ramipril if the patient is already in need of a blood pressure medication. Both treatment groups were effective at reducing blood pressure with 38.6% of patients in the ramipril and 39.7% of patients in the diuretic group achieving a blood pressure below 130/80 mmHg by the end of the study. The composite outcome of total mortality (ramipril cohort: 2.0%; thiazide diuretic cohort: 2.9%) and major cardiovascular events (ramipril cohort: 3.7%; thiazide diuretic cohort: 5.0%) between the ramipril and thiazide diuretic groups was statistically insignificant. However, when both mortality and cardiovascular events were grouped in a post-hoc Kaplan-Meier analysis, the ramipril cohort was determined to have significantly less outcomes compared to the thiazide diuretic (p = 0.033).

ACE-inhibitors have also been studied in the context of diabetes prevention. The “Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication” (DREAM) trial recruited 5,269 study subjects who had impaired fasting glucose but did not have baseline cardiovascular disease. Participants were randomized to receive either ramipril (up to 15 mg daily) or placebo concomitantly with rosiglitazone or placebo, and were followed for approximately 3 years. The primary outcome of the study was a composite endpoint of progression to diabetes or death. While ramipril therapy did not account for a significant difference in the primary outcome compared to placebo (p =0.15), it did help achieve normal plasma glucose levels in these patients (HR 1.16; 95% CI 1.07-1.27; p = 0.001). Due to the confounding use of rosiglitazone, DREAM’s researchers ruled out the possibility that the rosiglitazone arm was responsible for any of the above outcomes (relationship p >0.11). The ADA guidelines recommend the use of an ACE-inhibitor or ARB for the treatment of albuminuria and/or hypertension in patients with diabetes. The ADA does not recommend these medications for primary prevention of diabetic nephropathy in patients with normal blood pressure and urine albumin-to-creatinine ratio < 30 mg/g. In addition to controlling blood pressure, the results of the HOPE, ADA, and DREAM trials also suggest that using ACE-inhibitors in patients with prediabetes and concomitant hypertension or pre-hypertension can help to decrease their risk of developing diabetes and its related complications (Table 3). While ACE-inhibitor therapy is preferred based on the above trials, ARBs may be a potential option for patients unable to tolerate ACE-inhibitors. As there is a lack of evidence of ARB use in patients with prediabetes, this substitution should be reserved as second line therapy.

Patient education regarding the potential side effects of ACE inhibitors and ARBs is important. Some common side effects patients may experience with either of these medications include dry cough (typically more associated with ACE inhibitors), angioedema, orthostatic hypotension, headache and dizziness. Patients should be educated regarding the potential risks and benefits of their antihypertensive therapy in order to decrease adverse events and improve medication adherence. Patients should be started at the lowest dose and titrated slowly to assess for tolerability. Blood pressure should be measured at each clinic visit to assess for efficacy. A baseline serum creatinine and potassium concentration should be evaluated prior to starting therapy and periodically thereafter.

Immunizations
Immunizations are another important aspect of preventing complications associated with diabetes. Recommended immunizations for patients with diabetes are listed in the ADA Standards of Care and include the following recommended immunizations: influenza; pneumococcal; and hepatitis B (Table 3). These vaccines are necessary because hyperglycemia can cause fluid and electrolyte disturbances that impair the immune system leading to an increased risk for common infections like influenza and pneumonia. Because patients with prediabetes also suffer from elevated glucose levels, they may be at an increased risk for infection and should therefore be considered candidates for these vaccinations as well.

Pharmacists with access to electronic medical records can use this information to assess vaccination status and make recommendations when necessary. In the community setting, pharmacy staff can gather immunization information from patients themselves or call the patient’s physician to obtain immunization history. In many states, pharmacists can even provide some or all of these vaccines to patients. With the recent passage of Bill S. 413, pharmacist immunization opportunities in South Carolina are quickly changing. Bill S. 413 will determine if a specific vaccination can be administered by a pharmacist without a written order or prescription. Once approved, the Board
of Medical Examiners will issue written protocols to allow the vaccination to be administered by a pharmacist. Therefore, we encourage readers to follow state-based protocols and stay abreast of any changes regarding immunization expansion.

Conclusion
Diabetes is a multifaceted disease requiring multiple interventions to improve outcomes. As such, the progression from prediabetes to overt type 2 diabetes is also associated with comorbid diseases and an increased risk of cardiovascular events. Pharmacists and pharmacy technicians can play a very important role in identifying patients at risk of developing diabetes and provide appropriate therapeutic recommendations and patient counseling.

It is important that pharmacists are familiar with current evidence-based medicine and practice guidelines that support such recommendations. The current ADA recommendations for patients with prediabetes include lifestyle modifications such as diet, exercise, smoking cessation, as well as metformin therapy for specific patients. According to the DPP study, metformin should be considered in patients with prediabetes only if they are less than 60 years old with BMI ≥ 35 kg/m² and/or have a previous history of gestational diabetes. Additional guidelines from the AHA also suggest calculating a 10-year cardiovascular risk score in patients at high risk for cardiovascular events with subsequent recommendations for statin and aspirin therapy when appropriate. Furthermore, studies such as the HOPE, ADaPT and DREAM have shown benefit in using ACE inhibitors to prevent the onset of diabetes and its associated complications. Finally, immunizations are also an important part of preventing diabetes-associated complications with pharmacy staff playing a big role in screening, counseling and administration. By applying certain aspects of the ADA Standards of Care and ACC/AHA Cardiovascular Risk Guidelines to patients with prediabetes, the overall health of these patients can be improved and their risk of developing diabetes possibly reduced.

Based on all the evidence reviewed, it is the opinion of the authors that patients with prediabetes should receive immunizations and ACE inhibitor therapy in the same way as listed per the ADA Standards of Care recommendations for patients with diabetes. Aspirin and statin therapy should remain a patient specific decision based on a multitude of factors. Given the significant benefits seen with statin therapy, we favor at least a moderate-intensity statin for most patients with prediabetes if aged 40-75 years, with consideration of patient-specific factors including a discussion with the patient.

References
Table 1: Risk Factors for Prediabetes/Diabetes and Testing Recommendations for Asymptomatic Adults

Consider testing in adults with BMI ≥ 25 kg/m² (≥ 23 kg/m² in Asian Americans) PLUS 1 Additional Risk Factor

<table>
<thead>
<tr>
<th>Additional Risk Factors</th>
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<tbody>
<tr>
<td>Physical inactivity</td>
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<tr>
<td>1st degree relative with diabetes</td>
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<tr>
<td>African American, Latino, Native American, Asian American, Pacific Islander</td>
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<tr>
<td>Delivery of babies &gt; 9 lb at birth OR diagnosis of gestational diabetes</td>
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<td>BP ≥ 140/90 mmHg OR on antihypertensive therapy</td>
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<tr>
<td>HDL &lt; 35 mg/dL AND/OR TG &gt; 250 mg/dL</td>
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<tr>
<td>Polycystic ovary syndrome</td>
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<td>History of CVD</td>
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<td>A1c ≥ 5.7%, IGT, or IFG w/ previous testing</td>
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</table>

*Testing should begin at age 45 years for all overweight patients (BMI ≥ 25 kg/m² or ≥ 23 kg/m² in Asian Americans) even without additional risk factors.

**Normal test results should be followed by repeat testing at least every 3 years, with more frequent testing recommendations based on initial results and risk factors. Those diagnosed with prediabetes should receive yearly testing.

BMI: body mass index; CVD: cardiovascular disease; BP: blood pressure; HDL: high-density lipoprotein; TG: triglycerides

Table 2: Diagnostic Criteria for Prediabetes and Increased Risk for Diabetes

<table>
<thead>
<tr>
<th>Impaired fasting glucose (IFG)</th>
<th>FPG: 100 mg/dL - 125 mg/dL</th>
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<tbody>
<tr>
<td>Impaired glucose tolerance (IGT)</td>
<td>2-hr plasma glucose in the 75-gram OGTT: 140 mg/dL - 199 mg/dL</td>
</tr>
<tr>
<td>A1c</td>
<td>5.7 - 6.4%</td>
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*For IFG, IGT & A1c testing risk extends below and above the ranges listed, with risk becoming much greater at the upper limits of the range.

FPG: fasting plasma glucose; IFG: impaired fasting glucose; OGTT: oral glucose tolerance test; IGT: impaired glucose tolerance;
Table 3: Treatment Recommendations for Individuals with Prediabetes\textsuperscript{1,3,4,11}

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<thead>
<tr>
<th>Population</th>
<th>Treatment Recommendation</th>
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<tbody>
<tr>
<td>IFG, IGT, or A1c 5.7-6.4%</td>
<td>Lifestyle modifications including:</td>
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<td></td>
<td>• ~7% weight loss</td>
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<td></td>
<td>• moderate-intensity physical activity at least 150 min/week</td>
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<tr>
<td>IFG, IGT, or A1c 5.7-6.4%, especially if:</td>
<td>Lifestyle modifications (as indicated above)</td>
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<tr>
<td>• &lt; 60 years of age</td>
<td>PLUS</td>
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<tr>
<td>• BMI ≥35 kg/m\textsuperscript{2}</td>
<td>Metformin 850 mg twice daily</td>
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<tr>
<td>• Previous history of gestational diabetes</td>
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Consider Additional Therapies for Comorbid Conditions

| Therapy    | Indication                                                                 |
|------------|                                                                           |
| Aspirin    | • 10 year cardiovascular risk > 10% or previous history of CVD            |
|            | ○ Aspirin 81 mg daily                                                     |
| Statins    | • 10 year ASCVD risk < 7.5%:                                               |
|            | ○ moderate intensity statin                                                |
|            | (atorvastatin 10 mg, rosuvastatin 10 mg, simvastatin 20-40 mg)            |
|            | • 10 year ASCVD risk ≥ 7.5%:                                               |
|            | ○ high intensity statin therapy                                            |
|            | (atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily)                    |
| ACE Inhibitors | • Hypertension                        |
|            | ○ Goal BP: < 140/90 mmHg                                                   |
| Immunizations | • At risk for: Influenza, Pneumococcal, Hepatitis B infections            |

*ALL patients should be counseled on smoking cessation and nutrition

IFG: impaired fasting glucose; IGT: impaired glucose tolerance; A1c: glycated hemoglobin; BMI: body mass index; BP: blood pressure; CVD: cardiovascular disease ASCVD: atherosclerotic cardiovascular disease.
Self-Assessment Questions

1. MJ is a 46 yo, overweight (BMI =26 kg/m2) female with a past medical history of hyperlipidemia and gestational diabetes. Her lab values during two separate visits reveal a FPG of 115 mg/dL and an A1c of 6.0%. She is currently on no medications. Based on the DPP study, which treatment option is the most appropriate for MJ at this time?
   a. Lifestyle modifications including 5-10% weight loss and moderate intensity physical activity 30 minutes 3 to 4 times a week
   b. Metformin 850 mg twice daily alone
   c. Lifestyle modifications including 5-10% weight loss and moderate intensity physical activity 30 minutes daily plus Metformin 850 mg twice daily.
   d. No treatment interventions necessary

2. CD is a 58 yo male, nonsmoker, diagnosed with prediabetes (most recent A1c is 6.2%). His past medical history also includes hyperlipidemia (total cholesterol = 250, HDL = 20) and hypertension (BP = 145/90 mmHg). His only medication is Lisinopril 40 mg daily for hypertension. CD’s calculated 10 year ASCVD risk is 33.7%. Which statin therapy is most appropriate for CD based on the ACC/AHA Cardiovascular Risk Guidelines?
   a. Pravastatin 10 mg
   b. Atorvastatin 40 mg
   c. Simvastatin 10 mg
   d. Statin therapy is not recommended

3. After visiting his primary care provider’s office to discuss his CVD risk, CD stops by your pharmacy. He wants to know if there are any vaccines that he should get. Of note, CD has not received his flu shot this fall and has no allergies that would be a concern for vaccinations. Which of the following vaccinations are recommended by the ADA for patients with diabetes and should also be considered in patients with prediabetes like CD?
   a. Influenza vaccine
   b. Pneumococcal vaccine
   c. Hepatitis B vaccine
   d. All of the above
4. MM is a 45 yo overweight female (BMI =27 kg/m2) with a past medical history of CVD, hypertension, dyslipidemia and anxiety. Her family history includes a mother with diabetes and depression and a father with hypertension. MM works as a taxi driver and admits to a poor diet and no exercise. Which of the following components of MM’s medical history is considered a risk factor for prediabetes?
   a. Physical inactivity
   b. Family history of depression
   c. Family history of cardiovascular disease
   d. Anxiety

5. MM is being screened for prediabetes. Which of the following is positive for prediabetes in MM based on the ADA guidelines and would require a repeat test for confirmation?
   a. FPG= 85 mg/dL
   b. A1c = 4.5%
   c. FPG = 120 mg/dL
   d. 2 hr post OGTT plasma glucose 110 mg/dL

6. RJ is a 38 yo male with a past medical history of hypertension and prediabetes. His only medication is metformin 850 mg BID. He is currently working on improving his diet and exercise habits as recommended by the ADA guidelines, but his blood pressure is still uncontrolled at 150/90 mmHg. Based on evidence presented in the HOPE and ADaPT trials, which blood pressure medication is most appropriate to add to RJ’s current regimen.
   a. Ramipril
   b. Amlodipine
   c. Chlorthalidone
   d. Carvedilol

7. RJ presents to the pharmacy with a new prescription for ramipril 2.5 mg once daily. Which of the following potential side effects should you counsel him on regarding this new medication?
   a. Memory loss
   b. Orthostatic hypotension
   c. Vomiting
   d. Irritability

8. HM is a 65 yo male diagnosed today with prediabetes. His past medical history includes hypertension, COPD, dyslipidemia, and osteoarthritis. Most recent BMI is 28 kg/m2. His current medications include Spiriva, Advair, Albuterol, Lisinopril/HCTZ, Atorvastatin, and Ibuprofen. Which of the following is the most appropriate treatment regimen for HM based on the DPP study and ADA guidelines?
   a. Metformin 850 mg BID alone.
   b. Lifestyle interventions alone.
   c. Metformin 850 mg BID plus Lifestyle interventions
   d. No therapy is recommended due to the patient’s advanced age

Oath of a Pharmacist

“I promise to devote myself to a lifetime of service to others through the profession of pharmacy. In fulfilling this vow:

- I will consider the welfare of humanity and relief of suffering my primary concerns.
- I will apply my knowledge, experience, and skills to the best of my ability to assure optimal outcomes for my patients.
- I will respect and protect all personal and health information entrusted to me.
- I will accept the lifelong obligation to improve my professional knowledge and competence.
- I will hold myself and my colleagues to the highest principles of our profession’s moral, ethical and legal conduct.
- I will embrace and advocate changes that improve patient care.
- I will utilize my knowledge, skills, experiences, and values to prepare the next generation of pharmacists.
I take these vows voluntarily with the full realization of the responsibility with which I am entrusted by the public.”